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(12) **United States Patent**
Disingrini et al.(10) **Patent No.:** US 9,127,015 B2
(45) **Date of Patent:** Sep. 8, 2015(54) **TRICYCLOPYRAZOLE DERIVATIVES**(75) Inventors: **Teresa Disingrini**, Vanzago (IT); **Sergio Mantegani**, Milan (IT); **Mario Varasi**, Milan (IT)(73) Assignee: **NERVIANO MEDICAL SCIENCES S.R.L.**, Nerviano (IT)

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C07D 487/14 (2006.01)(52) **U.S. Cl.**CPC *C07D 487/14* (2013.01)(58) **Field of Classification Search**CPC A61K 31/437; C07D 471/14
USPC 514/293; 546/82

See application file for complete search history.

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(57)

ABSTRACT

Compounds which are tricyclopyrazole derivatives or pharmaceutically acceptable salts thereof, their preparation process and pharmaceutical compositions comprising them are disclosed; these compounds are useful in the treatment of diseases caused by and/or associated with an altered protein kinase activity such as cancer, viral infection, prevention of AIDS development in HIV-infected individuals, cell proliferative disorders, autoimmune and neurodegenerative disorders; also disclosed is a process under Solid Phase Synthesis conditions for preparing the compounds of the invention and chemical libraries comprising a plurality of them.

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TRICYCLOPYRAZOLE DERIVATIVES

This application is a national stage application filed under 35 U.S.C. 371 of PCT/EP2010/068129, filed Nov. 24, 2010. The present invention relates to certain substituted derivatives of tricyclopypyrazole compounds, which modulate the activity of protein kinases. The compounds of this invention are therefore useful in treating diseases caused by dysregulated protein kinase activity. The present invention also relates to methods for preparing these compounds, combinatorial libraries thereof, pharmaceutical compositions comprising these compounds, and methods of treating diseases utilizing pharmaceutical compositions comprising these compounds.

The malfunctioning of protein kinases (PKs) is the hallmark of numerous diseases. A large share of the oncogenes and proto-oncogenes involved in human cancers code for PKs. The enhanced activities of PKs are also implicated in many non-malignant diseases, such as benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

PKs are also implicated in inflammatory conditions and in the multiplication of viruses and parasites. PKs may also play a major role in the pathogenesis and development of neurodegenerative disorders.

For general reference to PKs malfunctioning or disregulation see, for instance, Current Opinion in Chemical Biology 1999, 3, 459-465 and Carcinogenesis 2008, 29, 1087-191.

Substituted hexahydroarylquinolizine derivatives useful as antidiabetics, antidepressants, antihypertensives, and inhibitors of blood platelet aggregation, are disclosed in EP154142 A in the name of Merck and Co.

Synthesis of 1H-imidazo[1,2-a]pyrazolo[3,4-c]pyridine derivatives are described in Chemical & Pharmaceutical Bulletin (1990), 38(9), 2352-6, without reporting any biological activity.

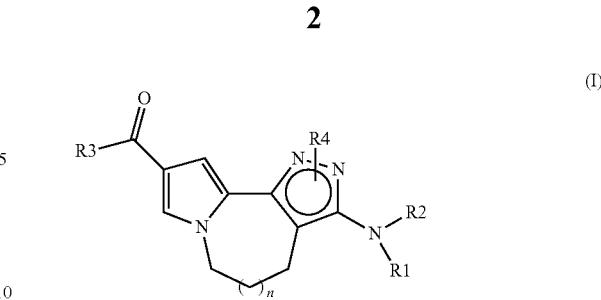
Tricyclic 5,6-dihydro-9H-pyrazolo[3,4-c]-1,2,4-triazolo [4,3- α]pyridine derivatives as phosphodiesterase inhibitors useful for the treatment of an inflammatory condition, asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis as well as AIDS, septic shock and other diseases, such as cachexia, are disclosed in WO9639408 in the name of Pfizer Inc.

Pyrrolo[2,1-a]isoquinolines, pyrrolo[1,2-a]quinolines, pyrrolo[2,1-a]isobenzazepines, and pyrrolo[1,2-a]benzazepines derivatives endowed with antineoplastic activity are described in Journal of Medicinal Chemistry (1988), 31(11), 2097-102.

Pyrrolo[2,1-a]isoquinolines as phosphodiesterase 10a inhibitors useful for treating cancer, are disclosed in WO2002048144 in the name of Bayer Aktiengesellschaft.

The present inventors have now discovered that the new compounds of formula (I), described below, are kinase inhibitors and are thus useful in therapy as antitumor agents.

Accordingly, a first object of the present invention is to provide a tricyclic compound represented by formula (I):



wherein

n is 0 or 1;

R1, R2 and R4, each independently one from the other, are selected from the group consisting of —R^a, —COR^a, —CONHR^a, —SO₂R^a and —COOR^a;

R3 is a group —NR^aR^b or —OR^a;

wherein R^a and R^b, the same or different, are each independently hydrogen or a group optionally substituted, selected from straight or branched C₁-C₆ alkyl, straight or branched C₂-C₆ alkenyl, straight or branched C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, cycloalkyl C₁-C₆ alkyl, heterocyclyl, heterocyclyl C₁-C₆ alkyl, aryl, aryl C₁-C₆ alkyl, heteroaryl and heteroaryl C₁-C₆ alkyl or, taken together with the nitrogen atom to which they are bonded, either R^a and R^b, may form an optionally substituted 3 to 8 membered heterocycle, optionally containing one additional heteroatom or heteroatomic group selected from S, O, N or NH, and pharmaceutically acceptable salts thereof.

The present invention also provides methods of synthesizing the substituted compounds, represented by formula (I), prepared through a synthetic process comprising well known reactions carried out according to conventional techniques, as well as through an extremely versatile solid-phase and/or combinatorial process.

The present invention also provides a method for treating diseases caused by and/or associated with dysregulated protein kinase activity, particularly ABL, ACK1, AKT1, ALK, AUR1, AUR2, BRK, BUB1, CDC7/DBF4, CDK2/CYCA, CHK1, CK2, EEF2K, EGFR1, EphA2, EphB4, ERK2, FAK, FGFR1, FLT3, GSK3beta, Haspin, IGFR1, IKK2, IR, JAK1, JAK2, JAK3, KIT, LCK, LYN, MAPKAP2, MELK, MET, MNK2, MPS1, MST4, NEK6, NIM1, P38alpha, PAK-4, PDGFR, PDK1, PERK, PIM1, PIM2, PKAalpha, PKCbeta, PLK1, RET, ROS1, SULU1, Syk, TLK2, TRKA, TYK, VEGFR2, VEGFR3, ZAP70.

A preferred method of the present invention is to treat a disease caused by and/or associated with dysregulated protein kinase activity selected from the group consisting of cancer, viral infection, prevention of AIDS development in HIV-infected individuals, cell proliferative disorders, autoimmune and neurodegenerative disorders.

Another preferred method of the present invention is to treat specific types of cancer including but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage including leukaemia, acute lymphocytic leukaemia, acute lymphoblastic leukaemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkitt's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukaemia; tumors of mesenchymal origin, including fibrosarcoma and rhab-

domyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Another preferred method of the present invention is to treat specific cellular proliferation disorders such as, for example, benign prostate hyperplasia, familial adenomatosis polyposis, neurofibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis, glomerulonephritis and post-surgical stenosis and restenosis.

The compounds of this invention may be useful in inhibiting tumour angiogenesis and metastasis, as well as in the treatment of organ transplant rejection and host versus graft disease.

The present invention further provides a method of treatment comprising a compound of formula (I) in combination with radiation therapy or chemotherapy regimen for simultaneous, separate or sequential use in anticancer therapy.

Moreover the invention provides an in vitro method for inhibiting protein kinase activity which comprises contacting the said protein kinase with an effective amount of a compound of formula (I).

The present invention also provides a pharmaceutical composition comprising one or more compounds of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, carrier or diluent.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) in combination with known cytostatic or cytotoxic agents, antibiotic-type agents, DNA damaging or intercalating agents, platinum-based agents, alkylating agents, antimetabolite agents, hormonal agents, antihormonal agents such as antiestrogens, antiandrogens and aromatase inhibitors, immunological agents, interferon-type agents, cyclooxygenase inhibitors (e.g. COX-2 inhibitors), matrixmetalloprotease inhibitors, tyrosine kinase inhibitors, other kinase inhibitors, anti-growth factor receptor agents, anti-HER agents, anti-EGFR agents, anti-angiogenesis agents (e.g. angiogenesis inhibitors), farnesyl transferase inhibitors, ras-raf signal transduction pathway inhibitors, cell cycle inhibitors, other cdks inhibitors, tubulin binding agents, topoisomerase I inhibitors, topoisomerase II inhibitors, inhibitors of kinesins, therapeutic monoclonal antibodies, inhibitors of mTOR, histone deacetylase inhibitors, inhibitors of hypoxic response and the like, for simultaneous, separate or sequential use in anticancer therapy.

Additionally, the invention provides a product or kit comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, or pharmaceutical compositions thereof and one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

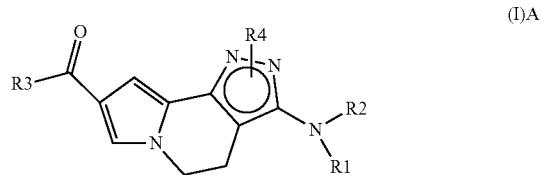
In yet another aspect the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, for use as a medicament.

Moreover the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, in the manufacture of a medicament with antitumor activity.

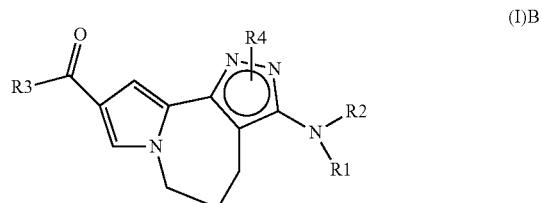
Finally, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, for use in a method of treating cancer.

As used herein, a compound of formula (I) wherein n is 0 and R1, R2, R3 and R4 are as defined above, namely 4,5-

dihydro-1H-pyrazolo[4,3-g]indolizine derivatives, may be represented by the general formula (I)A:



and a compound of formula (I) wherein n is 1 and R1, R2, R3 and R4 are as defined above, namely 1,4,5,6-tetrahydropyrazolo[3,4-c]pyrrolo[1,2-a]azepine derivatives, may be represented by the general formula (I)B:



Unless otherwise specified, when referring to the compounds of formula (I) per se as well as to any pharmaceutical composition thereof or to any therapeutic method of treatment comprising them, the present invention includes all the hydrates, solvates, complexes, metabolites, prodrugs, carriers, N-oxides and pharmaceutically acceptable salts of the compounds of this invention.

A metabolite of a compound of formula (I) is any compound into which this same compound of formula (I) is converted in vivo, for instance upon administration to a mammal in need thereof. Typically, without however representing a limiting example, upon administration of a compound of formula (I), this same derivative may be converted into a variety of compounds, for instance including more soluble derivatives like hydroxylated derivatives, which are easily excreted. Hence, depending upon the metabolic pathway thus occurring, any of these hydroxylated derivatives may be regarded as a metabolite of the compounds of formula (I).

Prodrugs are any covalently bonded compounds, which release the active parent drug according to formula (I) in vivo.

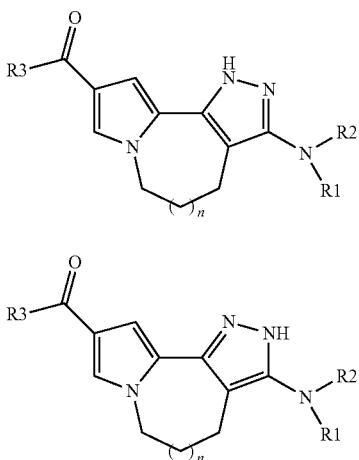
N-oxides are compounds of formula (I) wherein nitrogen and oxygen are tethered through a dative bond.

All forms of chiral isomers or other forms of isomers including enantiomers and diastereomers, are intended to be covered herein. Compounds containing a chiral center may be used as a racemic mixture or as an enantioselectively enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone.

In cases wherein compounds may exist in other tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

As such, unless otherwise provided, when in compounds of formula (I) n, R1, R2 and R3 are as defined above, R4 is hydrogen and only one of the following tautomeric forms of formula (I)a or (I)b is indicated, the remaining one has still to be intended as comprised within the scope of the invention:

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In the present description, unless otherwise indicated, with the term "straight or branched C₁-C₆ alkyl" we intend any group such as, for instance, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, and the like.

With the term "straight or branched C₂-C₆ alkenyl" or "straight or branched C₂-C₆ alkynyl" we intend any of the unsaturated alkenyl or alkynyl groups with from 2 to 6 carbon atoms for instance including vinyl, allyl, 1-propenyl, isopropenyl, 1-, 2- or 3-butenyl, pentenyl, hexenyl, ethynyl, 1- or 2-propynyl, butynyl, pentynyl, hexynyl, and the like.

With the term "C₃-C₆ cycloalkyl" we intend, unless otherwise specified, 3- to 6-membered all-carbon monocyclic ring, which may contain one or more double bonds but does not have a completely conjugated π -electron system. Examples of cycloalkyl groups, without limitation, are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexene and cyclohexadiene.

With the term "heterocycl" we intend a 3- to 7-membered, saturated or partially unsaturated carbocyclic ring where one or more carbon atoms are replaced by heteroatoms such as nitrogen, oxygen and sulfur. Non limiting examples of heterocycl groups are, for instance, pyrane, pyrrolidine, pyrrolidine, imidazoline, imidazolidine, pyrazolidine, pyrazoline, thiazoline, thiazolidine, dihydrofuran, tetrahydrofuran, 1,3-dioxolane, piperidine, piperazine, morpholine and the like.

With the term "aryl" we intend a mono-, bi- or poly-carbocyclic hydrocarbon with from 1 to 4 ring systems, optionally further fused or linked to each other by single bonds, wherein at least one of the carbocyclic rings is "aromatic", wherein the term "aromatic" refers to completely conjugated π -electron bond system. Non-limiting examples of such aryl groups are phenyl, α - or β -naphthyl or biphenyl groups.

With the term "heteroaryl" we intend aromatic heterocyclic rings, typically 5- to 7-membered heterocycles with from 1 to 3 heteroatoms selected among N, O or S; the heteroaryl ring can be optionally further fused or linked to aromatic and non-aromatic carbocyclic and heterocyclic rings. Not limiting examples of such heteroaryl groups are, for instance, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, imidazolyl, thiazolyl, isothiazolyl, pyrrolyl, phenyl-pyrrolyl, furyl,

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phenyl-furyl, oxazolyl, isoxazolyl, pyrazolyl, thienyl, benzothienyl, isoindolinyl, benzoimidazolyl, quinolinyl, isoquinolinyl, 1-phenyl-1,2,3-triazolyl, 2,3-dihydroindolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothiophenyl; benzopyranyl, 2,3-dihydrobenzoxazinyl, 2,3-dihydroquinoxalinyl and the like.

According to the meanings provided to R^a and R^b, any of the above groups may be further optionally substituted in any of their free positions by one or more groups, for instance 1 to 6 groups, selected from: halogen, nitro, oxo groups (=O), carboxy, cyano, C₁-C₆ alkyl, polyfluorinated alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, heterocycl, aryl, heteroaryl; amino groups and derivatives thereof such as, for instance, alkylamino, dialkylamino, arylamino, diarylamino, ureido, alkylureido or arylureido; carbonylamino groups and derivatives thereof such as, for instance, formylamino, alkylcarbonylamino, alkenylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino; hydroxy groups and derivatives thereof such as, for instance, alkoxy, polyfluorinated alkoxy, aryloxy, alkylcarbonyloxy, arylcarbonyloxy, cycloalkenyl-oxo or alkylideneaminoxy; carbonyl groups and derivatives thereof such as, for instance, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, cycloalkyloxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl; sulfured derivatives such as, for instance, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, arylsulfonyloxy, aminosulfonyl, alkylaminosulfonyl or dialkylaminosulfonyl.

In their turn, whenever appropriate, each of the above substituents may be further substituted by one or more of the aforementioned groups.

In the present description, unless otherwise specified, with the term "cyano" we intend a —CN residue.

With the term "nitro" we intend a —NO₂ group.

With the term "halogen" we intend a fluorine, chlorine, bromine or iodine atom.

With the term "polyfluorinated alkyl or alkoxy" we intend a straight or branched C₁-C₆ alkyl or alkoxy group as above defined, wherein more than one hydrogen atom is replaced by fluorine atoms such as, for instance, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethyl, 2,2,2-trifluoroethoxy, 1,2-difluoroethyl, 1,1,1,3,3,3-hexafluoropropyl-2-yl, and the like.

From all of the above, it is clear to the skilled man that any group which name has been identified as a composite name such as, for instance, cycloalkylalkyl, arylalkyl, heterocyclalkyl, alkoxy, alkylthio, aryloxy, arylalkyloxy, alkylcarbonyloxy and the like, has to be intended as conventionally construed from the parts to which it derives. So far, as an example, the terms heterocyclalkyl and cycloalkylalkyl stand for a straight or branched alkyl group being further substituted by a heterocyclic or cycloalkyl group, respectively, as above defined.

The term "pharmaceutically acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic,

nitric, carbonic, sulfuric, and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, trifluoroacetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzene-sulfonic, pantothenic, toluenesulfonic, 2-hydroxyethane-sulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, hydroxybutyric, galactaric and galacturonic acid. Suitable pharmaceutically acceptable base addition salts of the compounds of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methyl-glucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compounds of the present invention, for instance by reacting them with the appropriate acid or base.

A preferred class of compounds of formula (I) are the compounds wherein:

R1 is a group —CONHR^a wherein R^a is hydrogen or a group optionally substituted selected from straight or branched C₁-C₆ alkyl, straight or branched C₂-C₆ alkenyl, aryl and aryl C₁-C₆ alkyl.

Another preferred class of compounds of formula (I) are the compounds wherein:

R1 is a group —COR^a wherein R^a is hydrogen or a group optionally substituted selected from straight or branched C₁-C₆ alkyl, straight or branched C₂-C₆ alkenyl, aryl and aryl C₁-C₆ alkyl.

Another preferred class of compounds of formula (I) are the compounds wherein:

R1 is a group —SO₂R^a wherein R^a is hydrogen or a group optionally substituted selected from straight or branched C₁-C₆ alkyl, straight or branched C₂-C₆ alkenyl, aryl and aryl C₁-C₆ alkyl.

A further preferred class of compounds of formula (I) are the compounds wherein:

R2 is hydrogen.

A more preferred class of compounds of formula (I) are the compounds wherein:

R3 is a group —NR^aR^b wherein both of R^a and R^b are hydrogen or one of them is a hydrogen and the remaining one of R^a or R^b is a group optionally substituted selected from straight or branched C₁-C₆ alkyl, straight or branched C₂-C₆ alkenyl, aryl and aryl C₁-C₆ alkyl.

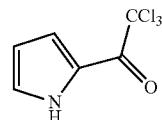
The most preferred class of compounds of formula (I) are the compounds wherein:

R4 is an hydrogen.

For a reference to any specific compound of formula (I) of the invention, optionally in the form of pharmaceutically acceptable salts, see the experimental section.

The present invention also provides a process for the preparation of a compound of formula (I) as defined above, characterized in that the process comprises the following steps:

a) reaction of the compound of formula (II):



(II)

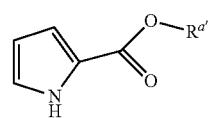
with an alcohol of formula (III)



(III)

wherein R^a' is straight or branched C₁-C₆ alkyl group;

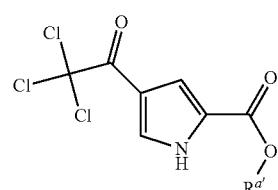
b) acylation by Friedel-Craft reaction of the resultant compound of formula (IV):



(IV)

wherein R^a' is as defined above;

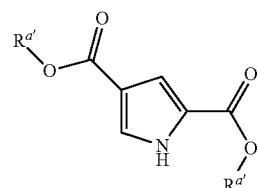
c) reaction of the resultant compound of formula (V):



(V)

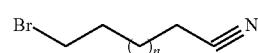
wherein R^a' is as defined above, with a suitable alcohol of formula (III) as defined above;

d) alkylation of the resultant compound of formula (VI):



(VI)

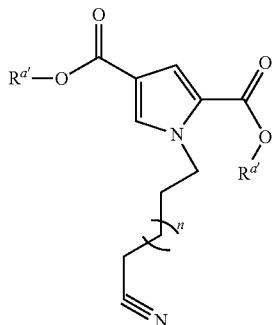
wherein both R^a' are independently as defined above, with suitable halo-cyanoalkane of formula (XXI):



(XXI)

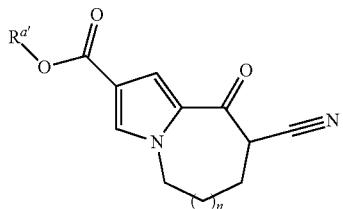
wherein n is 0 or 1;

e) intramolecular condensation of the resultant compound of formula (VII):

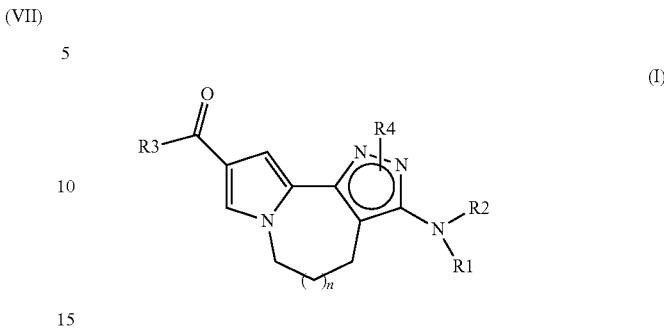


wherein n is as defined above and both R'a' are independently as defined above;

f) treatment with hydrazine or an hydrazine salt thereof, of the resultant compound of formula (VIII):



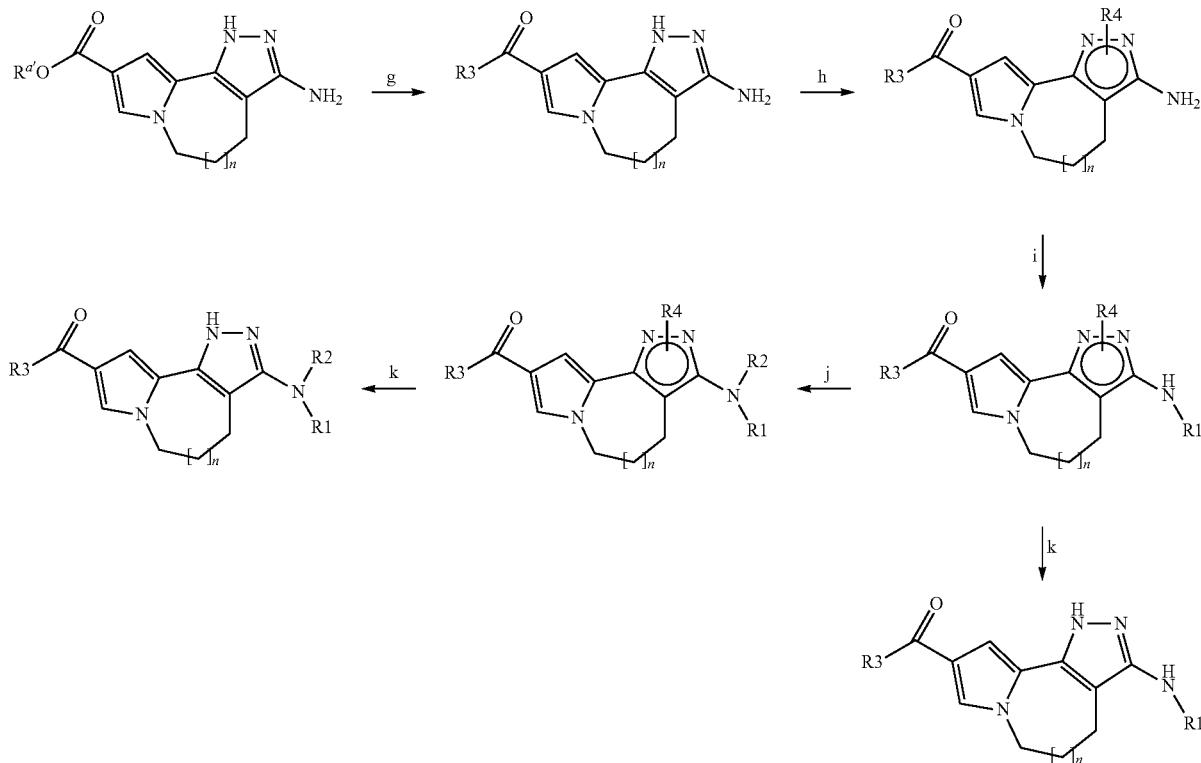
wherein n and R'a' are as defined above, to give a compound of formula (I):



wherein n is 0 or 1; R1, R2 and R4 are hydrogen and R3 is —OR'a', wherein R'a' is a straight or branched C₁-C₆ alkyl group; optionally separating the resultant compound of formula (I) into the single isomers; and/or converting the resultant compound of formula (I) into a different compound of formula (I) by replacing the group —OR'a' with a different group which R3 represents, and/or introducing the R4 group, and/or derivatizing the amino moiety; and/or removing the R4 group, and/or converting it into a pharmaceutically acceptable salt if desired.

Said optional conversions of a compound of formula (I) are summarized in scheme A below.

Scheme A



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wherein n, R1, R2, R3 and R4 are as defined above and R^a is straight or branched C₁-C₆ alkyl group.

The present invention further provides a process for the preparation of a compound of formula (I) as defined above, characterized in that the compound of formula (I) wherein n is as defined in formula (I);

R1, R2 and R4 are hydrogen, and R^a is straight or branched C₁-C₆ alkyl group, is optionally converted into the corresponding compound of formula (I) by replacing the group —OR^a with a different group which R3 represents, said conversion is carried out in step g) by one or more of the following reactions:

g.1) hydrolysis under basic condition to give the corresponding compound of formula (I) wherein R3 is OH, optionally followed by the coupling of the resultant compound with an amine of formula (IX):



wherein R^a and R^b are as defined in claim 1, to give the corresponding compound of formula (I) wherein R3 is —NR^aR^b, and R^a and R^b are as defined in claim 1;

g.2) transesterification by reactions with a compound of formula (III) as defined above, to give the corresponding compound of formula (I) wherein R3 is OR^a and R^a is a different C₁-C₆ alkyl;

g.3) coupling with an amine of formula (IX):



wherein R^a and R^b are as defined in formula (I), to give the corresponding compound of formula (I) wherein R3 is —NR^aR^b, and R^a and R^b are as defined in formula (I).

The present invention further provides a process for the preparation of a compound of formula (I) as defined above, characterized in that the compound of formula (I) wherein n and R3 are as defined in formula (I), and R1, R2 and R4 are hydrogen, is optionally converted into the corresponding compound of formula (I) by introducing the group R4, said conversion is carried out in step h) by one or more of the following reactions:

h.1) coupling with an equivalent of an halide of formula (X):



wherein R^a is as defined in formula (I) but not hydrogen and Z is a halogen, to give the corresponding compound of formula (I) wherein R4 is R^a, and R^a is as defined in formula (I) but not hydrogen;

h.2) coupling with an equivalent of an acyl halide of formula (XI):



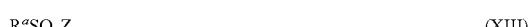
wherein R^a and Z are as defined above, to give the corresponding compound of formula (I) wherein R4 is —COR^a and R^a is as defined above;

h.3) coupling with an equivalent of an alcohoxy carbonyl halide of formula (XII):



wherein R^a and Z are as defined above, to give the corresponding compound of formula (I) wherein R4 is —OCOR^a and R^a is as defined above;

h.4) coupling with an equivalent of a sulfonyl halide of formula (XIII):



wherein R^a and Z are as defined above, to give the corresponding compound of formula (I) wherein R4 is —SO₂R^a and R^a is as defined above;

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h.5) coupling with an equivalent of an isocyanate of formula (XIV):



wherein R^a is as defined above, to give the corresponding compound of formula (I) wherein R4 is —CONHR^a and R^a is as defined above.

The present invention further provides a process for the preparation of a compound of formula (I) as defined above, characterized in that the compound of formula (I) wherein n and R3 are as defined in formula (I); R1 and R2 are hydrogen and R4 is as defined in formula (I) but not hydrogen, is optionally converted into the corresponding compound of formula (I) by derivatizing the amino moiety, said conversion is carried out in step i) by one or more of the following reactions:

i.1) coupling with an equivalent of an acyl halide of formula (XI):



wherein R^a is as defined in formula (I) but not hydrogen and Z is a halogen, to give the corresponding compound of formula (I) wherein one of R1 or R2 is hydrogen and the other one is —COR^a and R^a is as defined above;

i.2) coupling with an equivalent of an alkoxy carbonyl halide of formula (XII):



wherein R^a and Z are as defined above, to give the corresponding compound of formula (I) wherein one of R1 or R2 is hydrogen and the other one is —OCOR^a and R^a is as defined above;

i.3) coupling with an equivalent of a sulfonyl halide of formula (XIII):



wherein R^a and Z are as defined above, to give the corresponding compound of formula (I) wherein one of R1 or R2 is hydrogen and the other one is —SO₂R^a and R^a is as defined above;

i.4) coupling with an equivalent of an isocyanate of formula (XIV):



wherein R^a is as defined above, to give the corresponding compound of formula (I) wherein one of R1 or R2 is hydrogen and the other one is —CONHR^a and R^a is as defined above;

i.5) coupling with an equivalent of a carbonyl compound of formula (XV):



wherein R^a and R^b are as defined in formula (I), to give the corresponding compound of formula (I) wherein one of R1 or R2 is hydrogen and the other one is —COR^a and R^a is as defined above.

The present invention further provides a process for the preparation of a compound of formula (I) as defined above, characterized in that the compound of formula (I) wherein n and R3 are as defined in formula (I); one of R1 and R2 is hydrogen and the other is as defined in formula (I) but not hydrogen, and R4 is as defined in formula (I) but not hydrogen, is optionally converted into the corresponding compound of formula (I) by further derivatizing the amino moiety, said conversion is carried in step j) by one or more of the reaction described under steps i.1)-i.5) described above.

The present invention further provides a process for the preparation of a compound of formula (I) as defined above,

characterized in that the compound of formula (I) wherein n, R1, R2 and R3 are as defined in formula (I) and R4 is as defined in formula (I) but not hydrogen, is optionally converted into the corresponding compound of formula (I) by removing the group R4 by treatment with a basic solution to give the corresponding compound of formula I wherein R4 is hydrogen, said conversion is carried out in step k).

The above process is an analogy process which can be carried out according to well-known methods.

The starting materials of the process object of the present invention, comprehensive of any possible variant, as well as any reactant thereof, are known compounds and if not commercially available per se may be prepared according to well-known methods.

For example, the compound of formula (II) and (XXI) are commercially available.

The compounds of formula (III), (IX), (X), (XI), (XII), (XIII), (XIV), (XV) and (XXI) are either commercially available or known and easily obtained according to known methods, for a general reference see: Smith, Michael—March's Advanced Organic Chemistry: reactions mechanisms and structure—5th Edition, Michael B. Smith and Jerry March, John Wiley & Sons Inc., New York (N.Y.), 2001.

According to step a) of the process the 2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone is reacted with ethanol to obtain the ethyl 1H-pyrrole-2-carboxylate. This reaction can be conducted in a variety of ways and experimental conditions, which are widely known in the art for condensation reactions. For a general reference to the operative conditions see: Nishiwaki, E. et al, Heterocycles [HTCYAM] 1988, 27, 1945; Freedlander, R. S. et al, J Org Chem [JOCEAH] 1981, 46, 3519; Harbuck, J. W. et al, J Org Chem [JOCEAH] 1972, 37, 3618; and Booth, C et al, Tetrahedron Lett [TELEAY] 1992, 33 (3), 413. Preferably, the reaction is carried out in presence of a base like trialkyl amine, sodium or potassium carbonates, alkali hydroxide or alkali hydride. The solvent, in case is not the same ethanol, could be a suitable solvent such as THF, ACN, dioxane or mixture of them and the temperature raging from room temperature to reflux.

According to step b) of the process, the compound of formula (IV) is reacted with trichloroacetyl chloride in presence of strong lewis acid such as AlCl₃, ZnCl₂, Pyridine, FeCl₃ or Sm(OTf)₃ in a dry solvent as ether, DCM, THF. Preferably, the reaction is carried out at reflux temperature.

According to step c) of the process, the compound of formula (V) is reacted with ethanol and the reaction is carried out as described under step (a).

According to step d) of the process, the reaction of the compound of formula (VI) with the halo-cyanoalkane can be conducted in a variety of ways and experimental conditions, which are widely known in the art for condensation reactions. For a general reference to the operative conditions see: Stevens, C. V. et al, Tetrahedron Lett [TELEAY] 2007, 48 (40), 7108-7111 and Dumas, D. J., J Org Chem [JOCEAH] 1988, 53, 4650. Preferably, the reaction is carried out in presence of bases such as alkali carbonates, alkali hydride in a suitable solvent such as tetrahydrofuran, dichloromethane, acetonitrile, 1,4-dioxane or dimethylamide.

According to step e) of the process, the intramolecular condensation of the compound of formula (VII) can be conducted in a variety of ways and experimental conditions, which are widely known in the art. For a general reference see: Crowley, J. I. et al, J Am Chem Soc [JACSAT] 1970, 92, 6363-6365. Preferably the reaction is carried out according to the conditions of the Dieckmann reaction with potassium or sodium alkoxide in acetonitrile, tetrahydrofuran, toluene or an alcoholic solvent.

According to step f) of the process, the reaction between the compound of formula (VIII) and hydrazine or an hydrazine salt, can carried out in a variety of ways and experimental conditions, which are widely known in the art. Preferably, the reaction is carried out in the presence of catalytic amounts of an acid, for instance hydrochloric, acetic or sulphuric acid; in a suitable solvent such as, for instance, tetrahydrofuran, 1,4-dioxane, acetonitrile, methanol or ethanol; at a temperature ranging from about room temperature to reflux and for a time varying from about 30 minutes to about 8 hours.

According to any one of steps g.1) to g.3) of the process, the conversion of the alkoxy carbonyl derivative of formula (I) obtained in step e) into a different compound of formula (I) by replacing the group —OR' with a different group which R3 represents, can be carried out in a variety of ways, according to conventional methods.

According to step g.1) of the process, the hydrolysis under acid or basic condition of the alkoxy carbonyl derivative for conversion into the corresponding carboxylic acid derivative, 20 is conducted according to standard procedures as reported in The Chemistry of Carboxylic Acids and Esters, Saul Patai, Interscience Publisher (John Wiley&Sons 1969).

According to step g.2) of the process, the transesterification of the alkoxy carbonyl derivative is conducted according to standard procedures as reported in The Chemistry of Carboxylic Acids and Esters, Saul Patai, Interscience Publisher (John Wiley&Sons 1969).

According to step g.3) of the process, the coupling of the alkoxy carbonyl or the corresponding carboxylic acid derivative with an amine is conducted according to standard procedures as reported in The Chemistry of Amides, Saul Patai, Interscience Publisher (John Wiley&Sons 1970). Preferably, the reaction is carried out in the presence of a suitable condensing agent, for instance dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (EDC), 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine (HBTOH), O-benzotriazolyltetramethylisouronium tetrafluoroborate (TBTU), or benzotriazol-1-yloxytritypyrrolidinophosphonium hexafluorophosphate (PyBOP), in an appropriate solvent such as dichloromethane or dimethylformamide, under the setting well-known to skilled person.

According to any one of steps h.1) to h.5) of the process, the introduction of the group R4 can be carried out in a variety of ways, according to conventional methods.

The selective introduction of the R4 group on the pyrazole nitrogen in position 1 or 2, due to the tautomeric equilibrium, could be obtained working with a stoichiometric amount of the alkylating, acylating, carbonylating, sulphorilating agent or isocyanate of formula (X), (XI), (XII), (XIII), (XIV) respectively, so as to prevent the multi-derivatization even on the amino group in position 3. The reaction is conducted in a suitable solvent such as dichloromethane, dimethylformamide, tetrahydrofuran or dioxane without using a base that could cleave in situ the R4 substituent just inserted.

According to any one of steps i.1) to i.5) of the process, the derivatization of the amino moiety, can be carried out in a variety of ways, according to conventional methods. For reference see: The Chemistry of Amino Group, Saul Patai, Interscience Publisher (John Wiley&Sons 1968), or J. Am. Chem. or J. Am. Chem. Soc., 1971, 93, 2897, or Comprehensive Organic Synthesis, Trost B. N., Fleming L. (Eds. Pergamon Press: New York, 1991; Vol. 8).

Preferably, according to any one of steps i.1) to i.4) of the process, the compound of formula (I) is dissolved in a suitable solvent such as dichloromethane, dimethylformamide, tetrahydrofuran, 1,4-dioxane or the like, and a suitable base such

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as pyridine, triethylamine, diisopropylamine or sodium carbonate is added therein. The compound of formula (XI), (XII), (XIII) respectively, is then added and the mixture stirred for a time of about 2 hours to about 15 hours, at a temperature ranging from about 20° C. to about 80° C. In the case of isocyanate of formula (XIV) the use of the base is optional.

Preferably, according to step i.5) of the process, the compound of formula (I) is reacted with an aldehyde or ketone derivative of formula (XV) under reductive conditions. From the above, it is clear to the skilled man that by employing an aldehyde derivative of formula (XV) wherein one of R^a and R^b is hydrogen, the corresponding derivative wherein R1 is —CH₂R^a is obtained. Likewise, by employing a ketone derivative, the corresponding derivative wherein R1 is —CHR^aR^b, wherein R^a and R^b are as defined above but different from hydrogen, is obtained.

According to any one of steps j.1) to j.5) of the process, the further derivatization of the amino moiety, can be carried out in a variety of ways, according to conventional methods. It is clear to the person skilled in the art that the further derivatization of the amino moiety is carried out in the same conditions reported in the step i) described above, to obtain a bis-substitution on the nitrogen in position 3.

According to step k) of the process, the removal of the group R⁴, can be carried out in a variety of ways, according to conventional methods. Preferably, the removal can be carried out reacting the compound of formula (I) with a basic solution such as hydrazine, ammonia, metal hydroxide and so on. With strongest base condition also the imides eventually present in position 3 can be hydrolyzed.

A compound of formula (I) can also be transformed into a pharmaceutically acceptable salt according to standard procedures that are known to those skilled in the art. Alternatively, a compound of formula (I) that is obtained as a salt can be transformed into the free base or the free acid according to standard procedures that are known to the skilled person.

In addition to the above, the compounds of formula (I) may be advantageously prepared according to combinatorial chemistry techniques widely known in the art, by accomplishing the aforementioned reactions between the intermediates in a serial manner and by working under solid-phase synthesis (SPS) conditions.

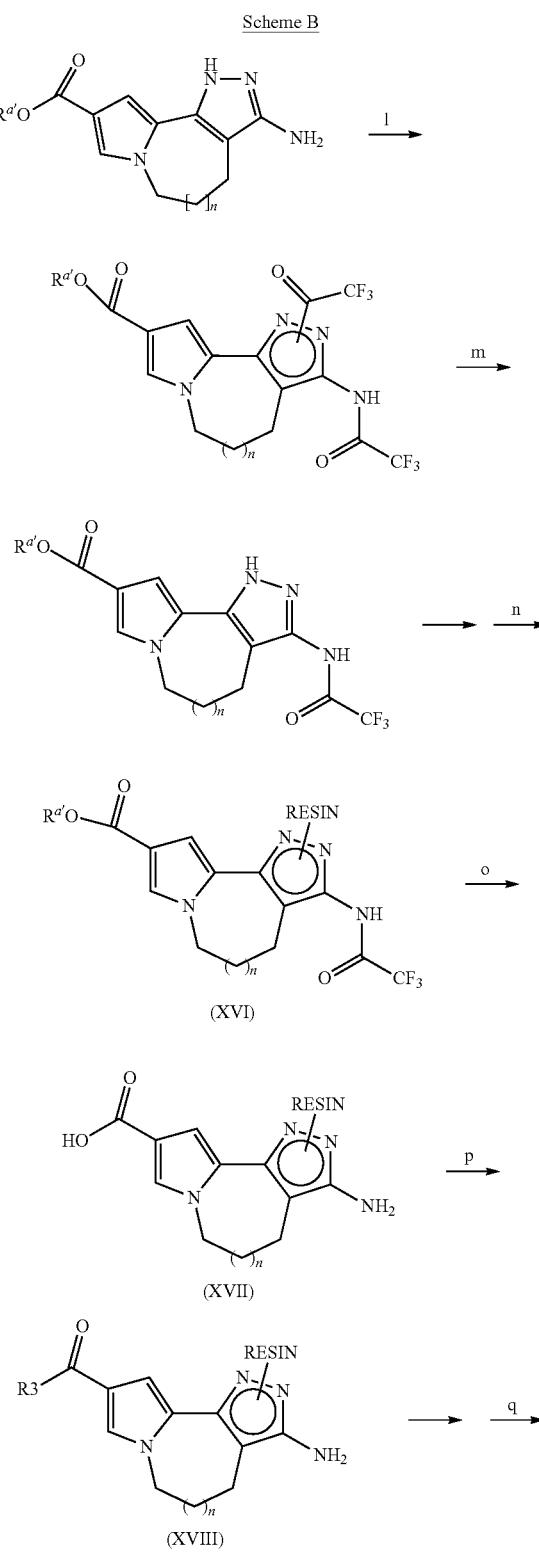
The present invention also provides a process for the preparation of a compound of formula (I) as defined above, characterized in that the process comprises the following steps:

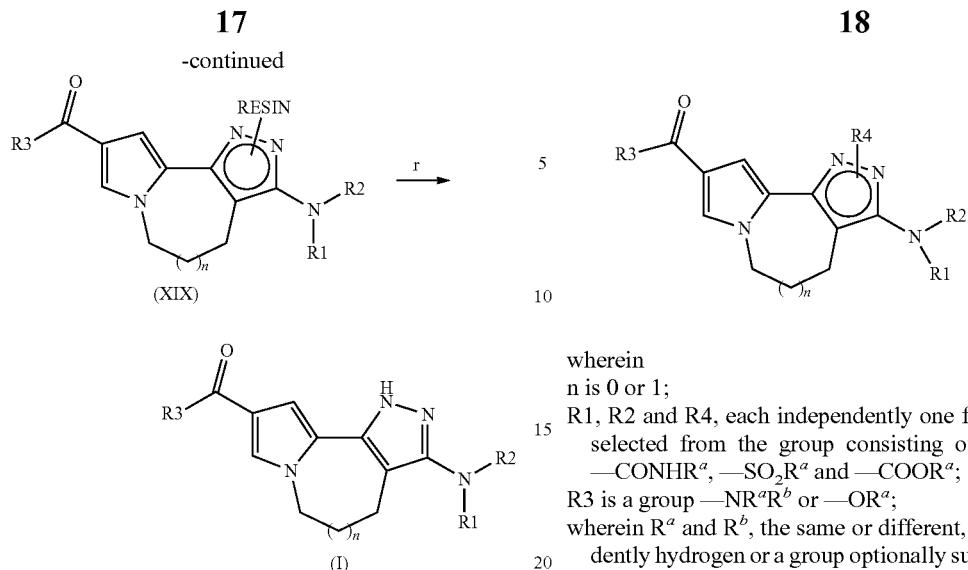
- l) acylation of the alkoxycarbonyl derivative of formula (I) obtained in step f) described above, with trifluoroacetic anhydride;
- m) removal from the resultant compound of the trifluoroacetyl group in position 1 or 2 of the pyrazolo ring;
- n) loading of the resultant compound of formula (I) trifluoroacetylated in position 3 onto a resin as suitable solid support, wherein the resin is a commercially available polystyrenic resin such as for instance, Br-Wang resin, Trityl resin, Cl-trityl resin, Merrifield resin, MAMP resin or isocyanate resin and derivatives thereof;
- o) hydrolyzing under acid or basic conditions the alkoxycarbonyl group and the trifluoroacetyl group of the resultant compound of formula (XVI);
- p) coupling the carboxyl group of the resultant compound of formula (XVII) with an amine of formula (IX) described above;
- q) derivatizing the amino moiety in position 3 of resultant compound of formula (XVIII);
- r) cleaving the resin from the resultant compound of formula (XIX), so as to obtain the desired compounds of formula I,

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optionally converting the resultant compound of formula (I) into a different compound of formula (I) and/or converting it into a pharmaceutically acceptable salt if desired.

Said solid-phase-synthesis (SPS) is summarized in scheme B below.





wherein the resin is a commercially available polystyrenic resin such as for instance, Br-Wang resin, Trityl resin, Cl-trityl resin, Merrifield resin, MAMP resin or isocyanate resin and derivatives thereof; n, R1, R2 and R3 are as defined in formula (I) and $R^{a'}$ is straight or branched C_1 - C_6 alkyl group.

Any of the above reactions is carried out according to known methods, by working as formerly reported, and allows obtaining compounds of formula (I) as set forth above.

Step 1) is carried out as described under step i.1).

Step m) is carried out as described under step k).

According to step n) the compound of formula (I) is loaded on the trityl chloride resin (copolystyrene-1% DVB) to obtain the compound of formula XVI. The loading reaction may be carried out in a suitable solvent such as dichloromethane or tetrahydrofuran and in the presence of a base such as triethylamine, pyridine, diisopropylamine and so on. The reaction is shacked in a time between 18 and 24 h at room temperature. For references see: M. A. Youngman, et al. Tetrahedron Lett., 1997, 38, 6347; K. Barlos, et al. Poster P316, 24th European Peptide Symposium, Edinburgh, 1996.

Step o) is carried out as described under step g.1).

Step p) is carried out as described under step g.3).

Step q) is carried out as described under step i) and j).

According to step (r), the cleavage of the resin is performed under acidic conditions in the presence of suitable acids such as, for instance, hydrochloric, trifluoroacetic, methanesulfonic or p-toluenesulfonic acid. Preferably the reaction is carried out using trifluoroacetic acid in dichloromethane as solvent.

Clearly, by working according to combinatorial chemistry techniques as formerly indicated, a plurality of compounds of formula (I) may be obtained.

Hence, it is a further object of the present invention a library of two or more compounds of formula (I), according to a preferred embodiment of the invention,

wherein
 n is 0 or 1;
 R1, R2 and R4, each independently one from the other, are selected from the group consisting of $-R^a$, $-COR^a$, $-CONHR^a$, $-SO_2R^a$ and $-COOR^a$;
 R3 is a group $-NR^aR^b$ or $-OR^a$;
 wherein R^a and R^b , the same or different, are each independently hydrogen or a group optionally substituted, selected from straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, cycloalkyl C_1-C_6 alkyl, heterocyclyl, heterocyclyl C_1-C_6 alkyl, aryl, aryl C_1-C_6 alkyl, heteroaryl and heteroaryl C_1-C_6 alkyl or, taken together with the nitrogen atom to which they are bonded, either R^a and R^b , may form an optionally substituted 3 to 8 membered heterocycle, optionally containing one additional heteroatom or heteroatomic group selected from S, O, N or NH, and pharmaceutically acceptable salts thereof.

For a general reference to the above libraries of compounds of formula (I) see the experimental section.

From all of the above, it is clear to the skilled person that once a library of such derivatives is thus prepared, for instance consisting of about a thousands of compounds of formula (I), the said library can be very advantageously used for screening towards given kinases, as formerly reported.

towards given kinases, as formerly reported.
See, for a general reference to libraries of compounds and uses thereof as tools for screening biological activities, J. Med. Chem. 1999, 42, 2373-2382; and Bioorg. Med. Chem. Lett. 10 (2000), 223-226.

PHARMACOLOGY

45 The inhibiting activity of putative kinase inhibitors and the potency of selected compounds is determined through a method of assay based on the use of the Kinase-Glo® Luminescent Kinase Assay (commercially available from Promega corporation and described in Koresawa, M. and Okabe, T.

50 (2004) High-throughput screening with quantitation of ATP consumption: A universal non-radioisotope, homogeneous assay for protein kinase. *Assay Drug Dev Technol.* 2, 153-60).

The depletion of ATP as a result of kinase activity can be monitored in a highly sensitive manner through the use of Kinase-Glo® or Kinase-Glo® Plus Reagent, which uses luciferin, oxygen and ATP as substrates in a reaction that produces oxyluciferin and light.

The short forms and abbreviations used herein have the following meaning:

ACN acetonitrile

BSA bovine serum albumine

Tris 2-Amino-2-(hydroxymethyl)-1,3-propanediol

Hepes N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic

65 acid)

DTT threo-1,4-Dime

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TertBuOK potassium tertbutoxy
 MTBE methyl tertiary butyl ether
 DIPEA diisopropylethylamine
 PyBOP benzotriazol-1-yloxytris(pyrrolidino)phosphonium
 exafluorophosphate
 EDC 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide
 DHBTOH 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriaz-
 ine
 TEA triethylamine
 TFA trifluoroacetic acid
 TFAA trifluoroacetic anhydride
 TMOF trimethyl orto formate
 DCE dichloroethane
 DCM dichloromethane
 DMF dimethylformamide
 DMSO dimethylsulfoxide
 HOBT hydroxybenzotriazole
 KDa kiloDalton
 mg milligram
 µg microgram
 ng nanogram
 L liter
 mL milliliter
 µL microliter
 M molar
 mM millimolar
 µM micromolar
 nM nanomolar

Kinase reaction conditions are target (enzyme) dependent and thus undergo individual adaptations. The Kinase-Glo® Luminescent Kinase Assay can be used with virtually any kinase and substrate combination.

Also the buffer conditions may vary depending on the kinase of interest (e.g. for PKA a composition of 40 mM Tris pH 7.5, 20 mM MgCl₂, 0.1 mg/ml BSA, in 50 µl final volume is used). Typically the range of ATP titration is 0.1 µM to 10 µM.

The optimal kinase substrate results in the greatest change in luminescence when comparing kinase reaction wells with no kinase wells.

The optimal amount of kinase is determined by making two fold serial dilutions across plates using the optimal amount of ATP and optimal kinase substrate. The optimal amount of kinase to use in subsequent compound screens and 1050 determinations is the amount required for luminescence to be within the linear range of the kinase titration curve (sigmoidal dose response).

Robotized Kinase-Glo® Assay

This assay was set up for the measurement of kinase activity and/or inhibition.

It is homogeneous, quick, radioactivity-free and suitable for all type of protein kinases, such as PLK family, ABL, ACK1, AKT1, ALK, AUR1, AUR2, BRK, CDC7/DBF4, CDK2/CYCA, CHK1, CK2, EE2FK, EGFR1, ERK2, FAK, FGFR1, FLT3, GSK3beta, IGFR1, IKK2, IR, JAK2, JAK3, KIT, LCK, LYN, MAPKAPK2, MELK, MET, MPS1, MST4, NEK6, NIM1, P38alpha, PAK-4, PDGFR, PDK1, PERK, PIM1, PIM2, PIM3, PKAalpha, PKCbeta, PLK1, RET, SULU1, SYK, TRKA, VEGFR2, VEGFR3 or ZAP70.

We established the assay in 384 well-plates: the test mix consisted of:

- 1) 3x Enzyme mix (done in Kinase Buffer 3x), 5 µl/well
- 2) 3x substrate and ATP mix (done in ddH₂O), 5 µl/well
- 3) 3x compound of formula (I) (diluted into ddH₂O-3% DMSO)-5 µl/well)

As an outcome, the percentage of inhibition at 10 µM was evaluated for each compound tested: see below for compound

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dilution and assay scheme. Each enzyme had its own buffer constitution, substrate type and concentration. Incubation time instead was 90 min for all targets.

Test compounds were received as a 1 mM solution in 100% DMSO into 96 well plates. The plates were diluted to 30 µM in ddH₂O, 3% DMSO; 4 plates are reorganized in 384 well plate by dispensing 5 µl of each 96 wp into the four quadrants of a 384wp. In well P23 and P24 the internal standard inhibitor staurosporine was added.

Assay Scheme

Test plates were first added with 5 µl of the compound dilution (30 µM, corresponding to 3x dilution) and then loaded onto a robotized station together with one reservoir for the Enzyme mix (3x) and one for the ATP mix (3x), specific for each target under study.

To start the assay, the robot aspirated 5 µl of ATP/Substrate mix, made an air gap inside the tips (5 µl) and aspirated 5 µl of Enzyme mix. The subsequent dispensation into the test plates allowed the kinase reaction to start after 3 cycles of mixing, done by the robot itself by up and down pipetting. At this point, the correct concentration was restored for all reagents.

The robot incubated the plates for 90 minutes at room temperature, and then stopped the reaction by pipetting 15 µl of Kinase-Glo® reagent into the reaction mix. Three cycles of mixing were done immediately after the addition of the reagent.

The principle of the Kinase-Glo® technique is the presence in the reagent mixture of oxygen, luciferin and luciferase enzyme: in the presence of ATP, remaining from the kinase reaction, oxi-luciferin is produced with the emission of light, directly dependent on the amount of ATP. For optimal performances of this technique, the kinase reaction should utilize at least 15-20% of the available ATP.

After another 60 minutes of incubation to stabilize the luminescent signal, the plates were read on a ViewLux® instrument. Data were analyzed using the software package Assay Explorer® that provided percent inhibition data.

As example herein are reported the assay conditions used for testing the compounds of formula (I) against ALKtide YFF APCo kinase;

ATP concentration: 1 µM
 Enzyme concentration: 100 nM
 Reaction buffer: Hepes 50 mM pH 7.5, MgCl₂ 5 mM, MnCl₂ 1 mM, DTT 1 mM, Na₃VO₄ 3 uM, 0.2 mg/ml BSA.

Assay procedure: add 5 µl compound of formula (I) (3x), add 5 µl ATP/S mix (3x) in buffer 1x; add 5 µl enzyme in buffer 2x+3xBSA; for the blank, add 5 µl buffer 2x+3xBSA without enzyme. After 90 minutes of incubation, add 15 µl/well of Kinase-Glo reagent. After 60-90 minutes of incubation to stabilize the luminescent signal, the plates are read on a ViuwLux instrument.

The inhibitory activity of putative kinase inhibitors and the potency of selected compounds were also determined using a trans-phosphorylation assay.

Specific peptide or protein substrates are trans-phosphorylated by their specific ser-thr or tyr kinase in the presence of ATP traced with ³³P-γ-ATP, and in the presence of their own optimal buffer and cofactors. At the end of the phosphorylation reaction, more than 98% unlabeled ATP and radioactive ATP is captured by an excess of the ion exchange dowex resin; the resin then settles down to the bottom of the reaction plate by gravity. Supernatant is subsequently withdrawn and transferred into a counting plate, then evaluated by β-counting.

Reaction conditions are target (enzyme) dependent and thus undergo individual adaptations. Also the buffer conditions may vary depending on the kinase of interest. The assay

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can be used with virtually any kinase and substrate combination and is suitable for all type of protein kinases, such as ABL, ACK1, AKT1, ALK, AUR1, AUR2, BRK, BUB1, CDC7/DBF4, CDK21CYCA, CHK1, CK2, EEF2K, EGFR1, EphA2, EphB4, ERK2, FAK, FGFR1, FLT3, GSK3beta, Haspin, IGFR1, IKK2, IR, JAK1, JAK2, JAK3, KIT, LCK, LYN, MAPKAPK2, MELK, MET, MNK2, MPS1, MST4, NEK6, NIM1, P38alpha, PAK-4, PDGFR, PDK1, PERK, PIM1, PIM2, PKAalpha, PKCbeta, PLK1, RET, ROS1, SULU1, Syk, TLK2, TRKA, TYK, VEGFR2, VEGFR3, ZAP70.

As example herein are reported the assay conditions used for testing the compounds of formula (I) against cdc7 and cdk2 kinase.

Inhibition Assay of Cdc7 Activity

The inhibiting activity of putative Cdc7 inhibitors and the potency of selected compounds is determined through a method of assay based on the use of Dowex resin capture technology.

The assay consists of the transfer of radioactivity labeled phosphate moiety by the kinase to an acceptor substrate.

The resulting ^{33}P -labeled product is separated from unreacted tracer, transferred into a scintillation cocktail and light emitted is measured in a scintillation counter.

The inhibition assay of Cdc7/Dbf4 activity is performed according to the following protocol.

The MCM2 substrate is trans-phosphorylated by the Cdc7/Dbf4 complex in the presence of ATP traced with $\gamma^{33}\text{P}$ -ATP. The reaction is stopped by addition of Dowex resin in the presence of formic acid. Dowex resin particles capture unreacted $\gamma^{33}\text{P}$ -ATP and drag it to the bottom of the well while ^{33}P phosphorylated MCM2 substrate remains in solution. The supernatant is collected, transferred into Optiplate plates and the extent of substrate phosphorylation is evaluated by β counting.

The inhibition assay of Cdc7/Dbf4 activity was performed in 96 wells plate according to the following protocol.

To each well of the plate were added:

10 μl test compound (10 increasing concentrations in the nM to uM range to generate a dose-response curve). The solvent for test compounds contained 3% DMSO. (final concentration 1%)

10 μl substrate MCM2 (6 M final concentration), a mixture of cold ATP (2 M final concentration) and radioactive ATP (1/5000 molar ratio with cold ATP).

10 μl enzyme (Cdc7/Dbf4, 2 nM final concentration) that started the reaction. The buffer of the reaction consisted in 50 mM HEPES pH 7.9 containing 15 mM MgCl₂, 2 mM DTT, 3 uM NaVO₃, 2 mM glycerophosphate and 0.2 mg/ml BSA.

After incubation for 60 minutes at room temperature, the reaction was stopped by adding to each well 150 μl of Dowex resin in the presence of 150 mM formic acid. After another 60 min incubation, 50 L of suspension were withdrawn and transferred into 96-well OPTI-PLATEs containing 150 μl of MicroScint 40 (Packard); after 5-10 minutes shaking the plates were read for 1 min in a Packard TOP-Count radioactivity reader.

IC50 determination: inhibitors were tested at different concentrations ranging from 0.0005 to 10 M. Experimental data were analyzed by the computer program Assay Explorer using the four parameter logistic equation:

$$y = \text{bottom} + (\text{top} - \text{bottom}) / (1 + 10^{(\log IC50 - x) * \text{slope}})$$

where x is the logarithm of the inhibitor concentration, y is the response; y starts at bottom and goes to top with a sigmoid shape.

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Inhibition Assay of Cdk2/Cyclin A Activity

Kinase reaction: 1.5 μM histone H1 substrate, 25 μATP (0.2 μCi P33-ATP), 30 ng of baculovirus co-expressed Cdk2/Cyclin A, 10 M inhibitor in a final volume of 100 μl buffer (TRIS HCl 10 mM pH 7.5, MgCl₂ 10 mM, 7.5 mM DTT) were added to each well of a 96 U bottom well plate. After 10 min at 37° C. incubation, reaction was stopped by 201 EDTA 120 mM.

Capture: 100 μl were transferred from each well to Multi-Screen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 μl /well PBS Ca++/Mg++-free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37° C., then 100 μl /well scintillant were added and ^{33}P labeled histone H1 was detected by radioactivity counting in the Top-Count instrument.

Results: Data are analysed by an internally customized version of the SW package "Assay Explorer" that provides either % inhibition for primary assays or sigmoidal fittings of the ten-dilutions curves for IC₅₀ determination in the secondary assays/hit confirmation routines.

As an example, in Table A are reported some compounds of the present invention which showed IC₅₀ of less 10 μM when tested against different kinases.

TABLE A

Entry	Code	IC ₅₀ (μM)	
		IC ₅₀ (μM)	Enzyme
35	190	A20-M1-B8	2.43 ABL
	193	A21-M1-B8	4.94 ABL
	200	A35-M1-B8	3.50 ABL
	10	A5-M1-B8	2.23 ABL
	390	A21-M1-B34	5.34 ABL
	397	A35-M1-B34	4.31 ABL
	400	A5-M1-B34	0.82 ABL
	434	A21-M1-B36	3.23 ABL
	467	A5-M1-B37	5.10 ABL
	561	A5-M1-B41	0.40 ABL
40	578	A5-M1-B42	1.79 ABL
	615	A5-M1-B43	0.54 ABL
	10	A5-M1-B8	1.86 ABL
	619	A38-M1-B41	2.29 ABL
	619	A38-M1-B41	0.92 ABL
	100	A5-M1-B25	1.92 ACK1
	120	A5-M1-B26	3.04 ACK1
	141	A5-M1-B27	2.40 ACK1
	163	A5-M1-B28	4.33 ACK1
	190	A20-M1-B8	1.04 ACK1
45	193	A21-M1-B8	0.63 ACK1
	196	A6-M1-B8	1.89 ACK1
	200	A35-M1-B8	0.49 ACK1
	10	A5-M1-B8	0.63 ACK1
	221	A35-M1-B10	3.13 ACK1
	224	A5-M1-B10	3.25 ACK1
	238	A21-M1-B17	1.41 ACK1
	246	A5-M1-B17	2.16 ACK1
	263	A35-M1-B30	6.56 ACK1
	266	A5-M1-B30	4.71 ACK1
50	307	A35-M1-B7	5.91 ACK1
	310	A5-M1-B7	1.43 ACK1
	331	A5-M1-B31	3.16 ACK1
	342	A20-M1-B32	3.06 ACK1
	351	A35-M1-B32	1.21 ACK1
	354	A5-M1-B32	1.38 ACK1
	390	A21-M1-B34	0.89 ACK1
	397	A35-M1-B34	1.08 ACK1
	400	A5-M1-B34	0.36 ACK1
	434	A21-M1-B36	3.34 ACK1
60	443	A5-M1-B36	4.12 ACK1
	467	A5-M1-B37	1.00 ACK1

TABLE A-continued

Entry	Code	IC ₅₀ (uM)	Enzyme
480	A21-M1-B38	2.04	ACK1
489	A5-M1-B38	2.16	ACK1
509	A35-M1-B39	2.85	ACK1
512	A5-M1-B39	1.94	ACK1
536	A5-M1-B40	1.73	ACK1
552	A21-M1-B41	2.45	ACK1
559	A35-M1-B41	2.87	ACK1
561	A5-M1-B41	0.96	ACK1
576	A35-M1-B42	2.20	ACK1
578	A5-M1-B42	0.44	ACK1
615	A5-M1-B43	1.01	ACK1
680	A5-M2-B26	4.84	ACK1
855	A5-M2-B31	3.51	ACK1
894	A35-M2-B33	3.82	ACK1
897	A5-M2-B33	2.47	ACK1
918	A33-M2-B34	1.44	ACK1
957	A35-M2-B36	3.98	ACK1
959	A5-M2-B36	0.74	ACK1
1020	A35-M2-B39	1.41	ACK1
1023	A5-M2-B39	0.55	ACK1
1024	A27-M2-B39	3.17	ACK1
1051	A21-M2-B41	1.56	ACK1
1055	A5-M2-B41	0.44	ACK1
10	A5-M1-B8	0.48	ACK1
619	A38-M1-B41	2.48	ACK1
1100	A38-M2-B41	2.82	ACK1
1055	A5-M2-B41	0.24	ACK1
619	A38-M1-B41	1.00	ACK1
200	A35-M1-B8	0.30	ACK1
397	A35-M1-B34	1.58	ACK1
620	A39-M1-B8	0.75	ACK1
621	A39-M1-B34	5.54	ACK1
397	A35-M1-B34	4.91	ALK
400	A5-M1-B34	5.81	ALK
615	A5-M1-B43	3.40	ALK
390	A21-M1-B34	5.06	BRK
397	A35-M1-B34	4.35	BRK
400	A5-M1-B34	0.86	BRK
467	A5-M1-B37	5.77	BRK
480	A21-M1-B38	6.30	BRK
561	A5-M1-B41	4.35	BRK
578	A5-M1-B42	3.64	BRK
615	A5-M1-B43	4.68	BRK
63	A16-M1-B18	2.99	CDC7/DBF4
63	A16-M1-B18	1.90	CDK2/CYCA
615	A5-M1-B43	7.87	EGFR1
397	A35-M1-B34	5.76	FGFR1
615	A5-M1-B43	7.27	FGFR1
63	A16-M1-B18	1.92	GSK3beta
190	A20-M1-B8	2.02	KIT
200	A35-M1-B8	3.52	KIT
400	A5-M1-B34	4.13	KIT
434	A21-M1-B36	5.03	KIT
561	A5-M1-B41	1.83	KIT
578	A5-M1-B42	6.61	KIT
615	A5-M1-B43	1.31	KIT
54	A8-M1-B16	2.68	KIT
26	A9-M1-B13	5.85	KIT
56	A9-M1-B16	0.85	KIT
58	A11-M1-B16	2.66	KIT
10	A5-M1-B8	5.98	KIT
63	A16-M1-B18	2.61	KIT
64	A16-M1-B19	4.47	KIT
397	A35-M1-B34	3.50	LCK
400	A5-M1-B34	3.99	LCK
434	A21-M1-B36	5.14	LCK
561	A5-M1-B41	1.15	LCK
615	A5-M1-B43	0.59	LCK
619	A38-M1-B41	4.13	LCK
200	A35-M1-B8	2.13	LYN
709	A32-M2-B28	3.09	MELK
752	A30-M2-B8	2.57	MELK
918	A33-M2-B34	1.23	MELK
976	A24-M2-B37	3.00	MELK
63	A16-M1-B18	6.33	MELK

TABLE A-continued

5	Entry	Code	IC ₅₀ (uM)	Enzyme
10	397	A35-M1-B34	4.17	PKCbeta
	709	A32-M2-B28	1.63	Syk
	752	A30-M2-B8	2.10	Syk
	1151	A42-M2-B33	3.15	Syk
	918	A33-M2-B34	0.48	Syk
	976	A24-M2-B37	2.78	Syk
15	397	A35-M1-B34	3.98	VEGFR3
	400	A5-M1-B34	4.94	VEGFR3
	665	A1-M2-B25	1.56	ZAP70
	709	A32-M2-B28	0.80	ZAP70
	752	A30-M2-B8	0.59	ZAP70
	1151	A42-M2-B33	1.83	ZAP70
20	918	A33-M2-B34	0.72	ZAP70
	976	A24-M2-B37	1.15	ZAP70

The compounds of the present invention can be administered either as single agents or, alternatively, in combination with known anticancer treatments such as radiation therapy or chemotherapy regimen in combination with cytostatic or cytotoxic agents, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents, cyclooxygenase inhibitors (e.g. COX-2 inhibitors), matrixmetalloprotease inhibitors, telomerase inhibitors, tyrosine kinase inhibitors, anti-growth factor receptor agents, anti-HER agents, anti-EGFR agents, anti-angiogenesis agents (e.g. angiogenesis inhibitors), farnesyl transferase inhibitors, ras-raf signal transduction pathway inhibitors, cell cycle inhibitors, other cdks inhibitors, tubulin binding agents, topoisomerase I inhibitors, topoisomerase II inhibitors, and the like.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within the approved dosage range.

Compounds of formula (I) may be used sequentially with known anticancer agents when a combination formulation is inappropriate.

The compounds of formula (I) of the present invention, suitable for administration to a mammal, e.g., to humans, can be administered by the usual routes and the dosage level depends upon the age, weight, conditions of the patient and administration route.

For example, a suitable dosage adopted for oral administration of a compound of formula (I) may range from about 10 to about 500 mg per dose, from 1 to 5 times daily. The compounds of the invention can be administered in a variety of dosage forms, e.g., orally, in the form tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form suppositories; parenterally, e.g., intramuscularly, or through intravenous and/or intrathecal and/or intraspinal injection or infusion.

The present invention also includes pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient, which may be a carrier or a diluent.

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a suitable pharmaceutical form. For example, the solid oral forms may contain, together with the active compound, diluents, e.g., lactose, dextrose saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g., silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding

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agents, e.g., starches, arabic gum, gelatine methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disintegrating agents, e.g., starch, alginic acid, alginates or sodium starch glycolate; effervescent mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. These pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be, e.g., syrups, emulsions and suspensions. As an example, the syrups may contain, as carrier, saccharose or saccharose with glycerine and/or mannitol and sorbitol.

The suspensions and the emulsions may contain, as examples of carriers, natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g., sterile water, olive oil, ethyl oleate, glycols, e.g., propylene glycol and, if desired, a suitable amount of lidocaine hydrochloride.

The solutions for intravenous injections or infusions may contain, as a carrier, sterile water or preferably they may be in the form of sterile, aqueous, isotonic, saline solutions or they may contain propylene glycol as a carrier.

The suppositories may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g., cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

With the aim of better illustrating the present invention, without posing any limitation to it, the following examples are now given.

EXPERIMENTAL SECTION

General Methods

Flash Chromatography was performed on silica gel (Merck grade 9395, 60A). The high-pressure liquid chromatography retention times (HPLC: r.t. values) were determined by:

HPLC Method 1A and 1B:

A Waters Alliance LC mod. 2795 equipped with a variable UV detector mod 2487, a Chemiluminescence Nitrogen detector (CLND, Antek 8060) and a Waters ZQ2000 mass detector (ESI interface) was used in this application. The total flow was splitted and distributed to the three detectors at a fixed ratio (64:15:21 UV:MS:CLND). The liquid chromatograph was equipped with a 30×3.0 mm I.D. column (Waters X-Bridge C18, 3.5 um particles), thermostated at 50° C. Two mobile phases were used: phase A was 0.05% w/v formic acid (1 mL/L of 50% formic acid Fluka 09676 in highly purified water) and phase B was 70/25/5 (v/v/v) MeOH/iPrOH/H₂O containing 0.035% w/v of formic acid (700 uL/L of 50% formic acid Fluka 09676).

A 5 μL volume of 1 mM nominal sample solution in DMSO was injected (sequential, partial loop mode with no air gaps) and a generic reversed phase gradient analysis was carried out at 0.8 mL/min into either a fast variant (method 1A) or a slower one (method 1B), as indicated in the following table:

Method 1A		Method 1B	
tR (min)	phase B (%)	tR (min)	phase B (%)
0.00	0	0.00	0
5.00	100	8.00	100
5.70	100	9.00	100

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-continued

Method 1A		Method 1B	
tR (min)	phase B (%)	tR (min)	phase B (%)
5.71	0	9.01	0
6.3	stop time	9.6	stop time
7.9	total analysis time (*)	11.2	total analysis time (*)

(*) between consecutive injections

10 The UV detector was operated at 220 nm, 5 Hz sampling rate. The MS device was operated at 3.2 kV capillary voltage, 30 V cone, 2 V extractor, 0.5 V RF lens, 400 L/hr desolvation flow, 100 L/hr cone flow, 100° C. source temperature, 150° C. 15 desolvation temperature, ESI(+) full scan 120-1200 amu acquisition, at 1.7 Hz sampling rate. The CLND detector was operated at 1050° C. furnace temp, 280 mL/min inlet oxygen flow, 80 mL/min inlet argon, 25 mL/min make-up argon, 30 mL/min ozone, 28 torr vacuum, 750 V PMT voltage, PMT 20 chamber at +10° C., sensitivity high, select 5, 4 Hz sampling rate.

HPLC Method 2:

25 HPLC-MS analyses were performed on a Finnigan MAT mod. LCQ ion trap mass spectrometer, equipped with an ESI (Electrospray) ion source, the mass spectrometer is directly connected to a HPLC SSP4000 (Thermo Separation) equipped with an autosampler Lc Pal (CTC Analytics) and an UV6000LP PDA detector.

HPLC Conditions:

30 Column: Phenomenex Gemini C18, 3 μm, 50×4.6 mm (default)

Temperature: 40° C.

Mobile phase A: Acetate Buffer 5 mM pH 4.5: acetonitrile 35 95:5 (v:v)

Mobile phase B: Acetate Buffer 5 mM pH 4.5: acetonitrile 5:95 (v:v)

Elution Gradient:

	Time (min)	% Mobile Phase A
40	0	100
	7	0
	9	0
45	11	100
	13	100

Flow rate: 1 mL/min

Injection volume: 10 μL

Column temperature: 40° C.

MS Conditions:

50 The LCQ mass spectrometer operates with an electrospray ionization (ESI) interface in positive and negative ion mode following the operation parameters reported in table 1. MS/MS experiments are performed on the most intense ion of each scan automatically by Xcalibur software. A 45% collision energy was used for the fragmentation of the precursor ions.

TABLE 1

Mass Spectrometer Instrument parameters		
	Parameter	Value
60	Capillary Temperature (° C.)	255
	Source Voltage (kV)	4.00
65	Capillary Voltage (V)	21.0

TABLE 1-continued

Mass Spectrometer Instrument parameters	
Parameter	Value
Tube Lens Offset (V)	-5.0
Multipole RF Amplifier (Vp-p)	400.0
Multipole 1 Offset (V)	-3.00
Multipole 2 Offset (V)	-6.50
InterMultipole Lens Voltage (V)	-16.00
Trap DC Offset Voltage (V)	-10.00
Full Micro scans	3
Full AGC Target Ions	5*10 ⁷
Full Max Ion Time (ms)	150
MSn Micro scans	3
MSn AGC Target Ions	2*10 ⁷
MSn Max Ion Time (ms)	200
Electron Multiplier (V)	-950.0

HPLC Method 3:

HPLC-MS analyses were performed on a Finnigan MAT mod. LCQ ion trap mass spectrometer, equipped with an ESI (Electrospray) ion source, the mass spectrometer is directly connected to a HPLC SSP4000 (Thermo Separation) equipped with an autosampler Lc Pal (CTC Analytics) and an UV6000LP PDA detector.

HPLC Conditions:

Column: Phenomenex Gemini C18, 3 µm, 50×4.6 mm (default)

Temperature: 40° C.

Mobile phase A: Acetate Buffer 5 mM pH 4.5: acetonitrile 95:5 (v:v)

Mobile phase B: Acetate Buffer 5 mM pH 4.5: acetonitrile 5:95 (v:v)

Elution Gradient:

Time (min)	% Mobile Phase A
0	100
2	80
9	60
10	0
12	0
12.10	100

Flow rate: 1 mL/min

Injection volume: 10 µL

Column temperature: 40° C.

MS Conditions:

The LCQ mass spectrometer operates with an electrospray ionization (ESI) interface in positive and negative ion mode following the operation parameters reported in table 1. MS/MS experiments are performed on the most intense ion of each scan automatically by Xcalibur software. A 45% collision energy was used for the fragmentation of the precursor ions.

TABLE 1

Mass Spectrometer Instrument parameters	
Parameter	Value
Capillary Temperature (° C.)	255
Source Voltage (kV)	4.00
Capillary Voltage (V)	21.0
Tube Lens Offset (V)	-5.0
Multipole RF Amplifier (Vp-p)	400.0
Multipole 1 Offset (V)	-3.00
Multipole 2 Offset (V)	-6.50

TABLE 1-continued

Mass Spectrometer Instrument parameters	
Parameter	Value
InterMultipole Lens Voltage (V)	-16.00
Trap DC Offset Voltage (V)	-10.00
Full Micro scans	3
Full AGC Target Ions	5*10 ⁷
Full Max Ion Time (ms)	150
MSn Micro scans	3
MSn AGC Target Ions	2*10 ⁷
MSn Max Ion Time (ms)	200
Electron Multiplier (V)	-950.0

Retention times (HPLC r.t.) are given in minutes at 220 nm or at 254 nm. Mass is given as m/z ratio.

When necessary, the compounds have been purified by preparative HPLC on a Waters X-Bridge Prep Shield RP18 (19×100 mm, 5 µm) column or a Phenomenex Gemini C18 (21.2×250 mm, 10 µm) column, using a Waters FractionLynx Autopurification System equipped with a 996 Waters PDA detector and a Micromass mod. ZQ single quadrupole mass spectrometer, electron spray ionization, positive mode. Mobile phase A was water 0.05% NH3/acetonitrile 95:5, and Mobile phase B was acetonitrile. Gradient from 10 to 90% B in 8 min or 15 min. Flow rate 20 mL/min.

¹H-NMR spectrometry was performed on a Bruker AVANCE 400 MHz single bay instrument with gradients. It is equipped with a QNP probe (interchangeable 4 nuclei probe—¹H, 13C, 19F and 31P) (NMR method 1) or on a Mercury VX 400 operating at 400.45 MHz equipped with a 5 mm double resonance probe [1H (15N-31P) ID_PFG Varian] (NMR method 2).

The compounds of formula (I), having an asymmetric carbon atom and obtained as racemic mixture, were resolved by HPLC separation on chiral columns. In particular, for example, preparative columns CHIRALPACK® AD, CHIRALPACK® AS, CHIRALCELL® OJ can be used.

As formerly indicated, several compounds of formula (I) of the invention have been synthesized, according to solution and combinatorial chemistry techniques.

In this respect, some compounds thus prepared have been conveniently and unambiguously identified, as per the coding system of tables III together with HPLC retention time (methods 1A, 1B, 2 and 3) and mass.

Each code, which identifies a single specific compound of formula (I), consists of three units A-M-B.

A represents any substituent R1 and R2—[see formula (I)] and is attached to the M central core through the nitrogen in position 3; each A substituent is represented in the following table I.

B represents any substituent R3 [see formula (I)] and is attached to the rest of the M central core through the carbon atom of the carbonyl group; each B substituent is represented in the following table II.

M refers to the central core, more precisely M1 represents 4,5-dihydro-1H-pyrazolo[4,3-g]indolizine core [see formula (I)A] whereas M2 represents 1,4,5,6-tetrahydropyrazolo[3,4-c]pyrrolo[1,2-a]azepine core [see formula (I) B]; each cores being substituted in position 3 by groups A and at the carbonyl group by groups B, substantially as follows:

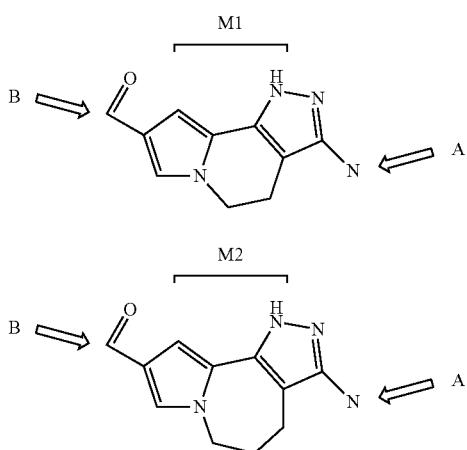
29**30**

TABLE I-continued

	FRAGMENT	CODE
5		A1
10		A2
15		A3
20		A4
25		A5
30		A6
35		A7
40		A8
45		A9
50		A10
55		A11

For ease of reference, each A and B groups of tables I and II has been identified with the proper chemical formula also indicating the point of attachment with the rest of the molecule M1 or M2.

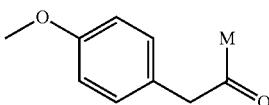
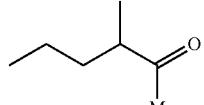
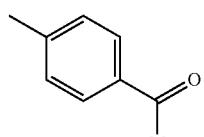
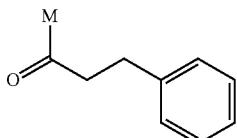
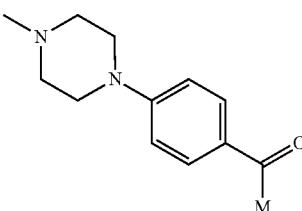
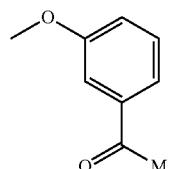
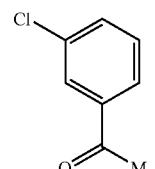
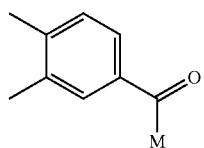
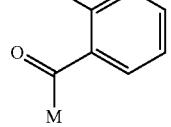
Just as an example, the compound A1-M1-B1 (entry 1 of table III) represents a 4,5-dihydro-1H-pyrazolo[4,3-g]indolizine (central core M1), being substituted at the nitrogen in 3-position by the group A1 and at the carbonyl group by the group B1; likewise, the compound A44-M2-B28 (entry 1116 of table III) represents a 1,4,5,6-tetrahydropyrazolo[3,4-c]pyrrolo[1,2-a]azepine (central core M2), being substituted at the nitrogen in 3-position by the group A44 and at the carbonyl group by the group B28.

TABLE I

	A groups
40	
45	

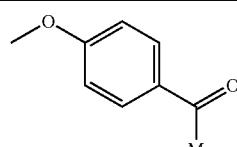
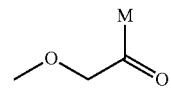
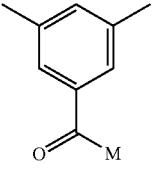
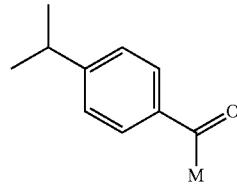
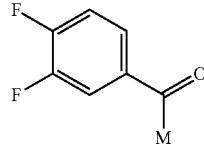
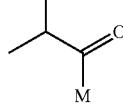
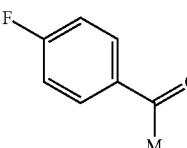
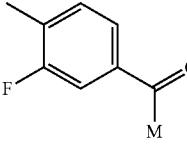
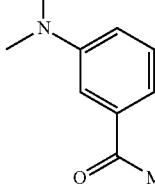
31

TABLE I-continued

	A12	
	A13	5
	A14	10
	A15	15
	A16	20
	A17	25
	A18	30
	A19	35
	A20	40
	A21	45
		50
		55
		60
		65

32

TABLE I-continued

	A22	
	A23	
	A24	
	A25	
	A26	
	A27	
	A28	
	A29	
	A30	
	A31	

33

TABLE I-continued

	A32	
	A33	5
	A34	10
	A35	15
	A36	20
	A37	25
	A38	30
	A39	35
	A40	40
	A41	45
		50
		55
		60
		65

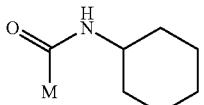
34

TABLE I-continued

	A42	
	A43	5
	A44	10
	A45	15
	A46	20
	A47	25
	A48	30
	A49	35
	A50	40
	A51	45
	A52	50
	A53	55

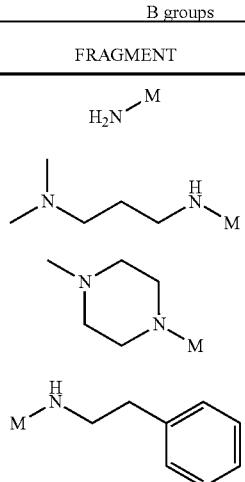
35

TABLE I-continued



A54

TABLE II



CODE

B1

B2

B3

B4

B5

B6

B7

B8

B9

B10

B11

B12

5

10

15

20

25

30

35

40

45

50

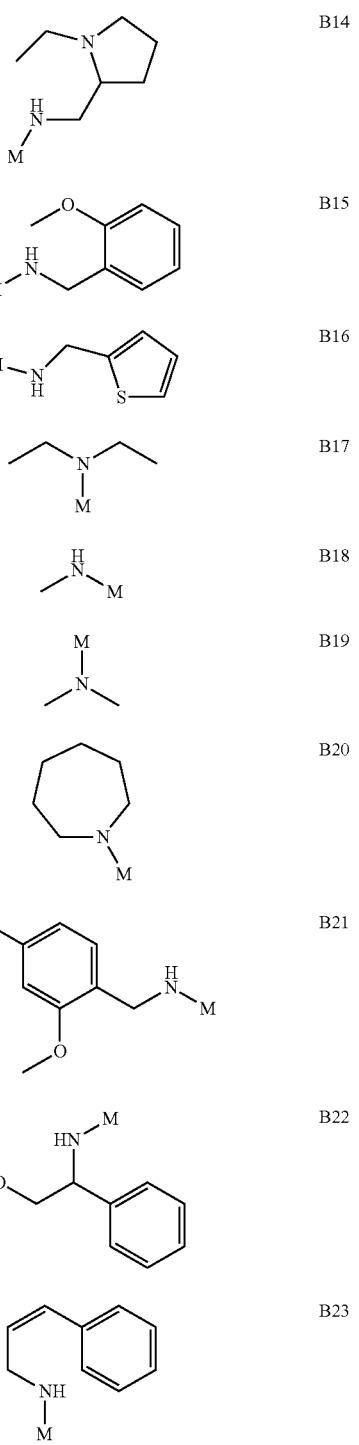
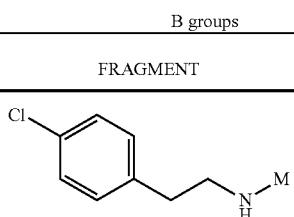
55

60

65

36

TABLE II-continued



37

TABLE II-continued

B groups	
FRAGMENT	CODE
	B24
	B25
	B26
	B27
	B28
	B29
	B30
	B31
	B32
	B33
	B34
	B35

38

TABLE II-continued

B groups	
FRAGMENT	CODE
	B36
	B37
	B38
	B39
	B40
	B41
	B42
	B43

Preparation 1

Preparation of Ethyl 1H-pyrrole-2-carboxylate (IV,
Wherein Ra' is $-\text{CH}_2-\text{CH}_3$)

A solution of 2,2,2-trichloro-1-(1H-pyrrol-2-yl)-ethanone (25 g, 0.12 mol) in ethanol (200 mL) was treated with potassium carbonate (5 g). The mixture was then heated to reflux 50 for 1 hour. After this time the residue solid was filtered off, and the solution concentrated under reduced pressure. Ethyl acetate (200 mL) was added and washed 2 times with water. The organic phase was dried with anhydrous sodium sulphate to obtain a pale yellow solid (18 g). HPLC (Method 2): m/z 55 140.12 [M+H]⁺ @ Rt=4.01 min. 1H NMR (400 MHz, DMSO-d₆) δ ppm 1.29 (t, J=7.07, 3 H) 4.23 (q, J=7.07, 2 H) 6.04-6.25 (m, 1 H) 6.65-6.86 (m, 1 H) 7.00-7.06 (m, 1 H) 11.83 (br. s., 1 H)

Preparation 2

Preparation of Ethyl
4-(trichloroacetyl)-1H-pyrrole-2-carboxylate (V,
Wherein Ra' is $-\text{CH}_2-\text{CH}_3$)

To ethyl 1H-pyrrole-2-carboxylate (18 g, 0.12 mol) dissolved in DCM (200 mL), was added anhydrous AlCl₃ (40 g).

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After 10 minutes of vigorous stirring was added drop wise a solution of trichloro-acetyl chloride (20 mL) in DCM (100 mL). The reaction was heated to reflux for 3 hours. The mixture was then allowed to reach room temperature and poured in a 2 L backer with iced HCl 6N left stirring for 2 hours. The DCM was extract and washed 2 times with NaHCO₃ and water. A dark solid was obtained which was not purified. HPLC (Method 2): m/z 282.45 [M-H] @ Rt=6.55 min. 1H NMR (400 MHz, DMSO-d6) δ ppm 1.32 (s, J=7.07 Hz, 3 H) 4.30 (s, J=7.07 Hz, 2 H) 7.26-7.40 (m, 1 H) 7.85-8.09 (m, 1 H) 13.06 (br. s., 1 H).

Preparation 3

Preparation of Diethyl 1H-pyrrole-2,4-dicarboxylate
(VI, Wherein Both of Ra' are —CH₂—CH₃)

To a solution of ethyl 4-(trichloroacetyl)-1H-pyrrole-2-carboxylate (30 g, 0.12 mol) in ethanol (250 mL) was added potassium carbonate (7 g). The mixture was then heated to reflux for 1 hour. After this time the residue solid was filtered off, and the solution concentrated under vacuum. Ethyl acetate (200 mL) was added and washed 2 times with water. The organic phase was dried with anhydrous sodium sulphate to obtain a brown solid (28 g).

HPLC (Method 2): m/z 212.34 [M+H]+@ Rt=4.79 min. 1H NMR (400 MHz, DMSO-d6) δ ppm 1.26 (t, J=7.07 Hz, 3H) 1.28 (t, J=7.07 Hz, 3H) 4.19 (q, J=7.11 Hz, 2 H) 4.25 (q, J=7.07 Hz, 2 H) 7.06 (dd, J=2.50, 1.65 Hz, 1 H) 7.54 (dd, J=3.35, 1.65 Hz, 1 H) 12.50 (br. s., 1 H)

Preparation 4

Preparation of Diethyl 1-(3-cyanopropyl)-1H-pyrrole-2,4-dicarboxylate (VII, Wherein n is 0 and Both of Ra' are —CH₂—CH₃)

To diethyl 1H-pyrrole-2,4-dicarboxylate (28 g, 0.13 mol) dissolved in ACN was added 30 g of potassium carbonate (0.21 mol) and 17 mL of 4-bromo-butynitrile (0.14 mol, d=1.3). The reaction was refluxed over night. The solvent was then evaporated under reduced pressure, the residue dissolved in ethyl acetate and washed 2 times with water. The crude was purified with a silica column (10 p silica) eluent cycloesane/ethyl acetate 7:3. 20 g of a white solid was obtained.

HPLC (Method 2): m/z 296.51 [M+NH4]+@ Rt=5.88 min. 1H NMR (400 MHz, DMSO-d6) δ ppm 1.24 (t, J=7.07 Hz, 3H) 1.27 (t, J=7.07 Hz, 3H) 2.03 (m, 2H) 2.48 (t, J=7.19 Hz, 2H) 4.19 (q, J=7.07 Hz, 2 H) 4.24 (q, J=7.07 Hz, 2 H) 4.38 (t, J=7.19 Hz, 2H) 7.16 (d, J=1.95 Hz, 1 H) 7.80 (d, J=1.83 Hz, 1 H)

Preparation 5

Preparation of Ethyl 7-cyano-8-oxo-5,6,7,8-tetrahydroindolizine-2-carboxylate (VIII, Wherein n is 0 and Ra' is —CH₂—CH₃)

To the diethyl 1-(3-cyanopropyl)-1H-pyrrole-2,4-dicarboxylate (7 g) dissolved in anhydrous THF (150 mL), under nitrogen atmosphere, a solution of TertBuOK 1N in THF (50 mL) was added drop wise. The reaction was left stirring. After 15 minutes water and citric acid were added (pH=5), after 30 minutes of vigorous stirring the solution was extract with 100 mL of ethyl acetate. The organic phase was then washed with water and NaHCO₃ (pH=10) dried on anhydrous Na₂SO₄. 5 g of a white solid were obtained (yield 87%). HPLC (Method

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2): m/z 250.31 [M+NH4]+@ Rt=4.23 min. 1H NMR (400 MHz, DMSO-d6) (mixture of tautomers cheto/enolic form ratio 56:44) δ ppm 1.26 (t, J=7.07 Hz, 3 H 56%) 1.28 (t, J=7.07 Hz, 3 H 44%) 2.62 (m, 2 H) 4.06 (t, J=6.83 Hz, 2 H 44%) 4.17 (q, J=7.07 Hz, 2 H 56%) 4.20 (q, J=7.07 Hz, 2 H 44%) 4.38 (dt, J=12.19 J=4.02 Hz, 2 H 56%) 4.51 (dd, J=11.24 J=5.08 Hz, 1 H 56%) 7.00 (d, J=1.59 Hz, 1H 44%) 7.23 (d, J=1.71, 1 H 56%) 7.65 (d, J=1.59, 1H 44%) 7.85 (d, J=1.59, 1H 56%) 10.96 (s, 1H 44% OH enolic)

Example 1

Preparation of the Ethyl 3-amino-4,5-dihydro-1H-pyrazolo[4,3-g]indolizine-8-carboxylate (I, Wherein n is 0, R1, R2 and R4 are Hydrogen, and R3 is —O—CH₂—CH₃)

To ethyl 7-cyano-8-oxo-5,6,7,8-tetrahydroindolizine-2-carboxylate (12 g, 52 mmol) in ethanol a solution of hydrazine monohydrate (6.5 g, 130 mmol) and acetic acid (9 g, 150 mmol) was added. The reaction was refluxed for 62 hours and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and NH₃. The organic phase was dried on Na₂SO₄. 10 g of a pale yellow solid were obtained (yield 78%).

HPLC(Method 2): m/z 247.25 [M+H]+@ Rt=3.17 min. 1H NMR (400 MHz, DMSO-d6) δ ppm 1.25 (t, J=7.13 Hz, 3 H) 2.69 (t, J=6.71 Hz, 2 H) 4.05 (t, J=6.71 Hz, 2 H) 4.17 (q, J=7.07 Hz, 2 H) 4.40-5.13 (m, 2 H) 6.48 (br. s., 2H) 7.49 (s, 1 H) 11.49 (br. s., 1 H)

Example 2

Preparation of Compound Ethyl 3-[(trifluoroacetyl)amino]-4,5-dihydro-1H-pyrazolo[4,3-g]indolizine-8-carboxylate (I, Wherein n is 0, R1 is —COCF₃, R2 and R4 are Hydrogen, and R3 is —O—CH₂—CH₃)

To the compound ethyl 3-amino-4,5-dihydro-1H-pyrazolo[4,3-g]indolizine-8-carboxylate (5 g, 20.3 mmol) in DCM, was added TEA (11 g, 110 mmol) and TFAA (21 g 100 mmol). The reaction mixture was stirred at room temperature for 3 hours and then concentrated in vacuo. To the residue diluted NH₃ and MeOH were added and stirred for 1 hour. The solution was then concentrated. 100 mL of water was added and extracted with ethylacetate (3×100 mL).The organic phase was dried with anhydrous sodium sulphate to obtain a pale yellow solid (6.5 g, 92%).

LCMS (HPLC Method 2): m/z 343 [M+H]+@ Rt 4.75 min (100% by ELS detection).

1H NMR (400 MHz, DMSO-D6) δ ppm 13.13 (s, 1 H) 11.61 (s, 1 H) 7.62 (s, 1 H) 6.68 (s, 1 H) 4.21 (q, J=7.07 Hz, 2 H) 4.13 (t, J=6.83 Hz, 2 H) 2.81 (t, J=6.77 Hz, 2 H) 1.28 (t, J=7.13 Hz, 3 H)

Preparation 6

Preparation of Solid Supported 3-amino-4,5-dihydro-1H-pyrazolo[4,3-g]indolizine-8-carboxylic acid (XVII, Wherein n is 0)

To polystyrene trityl chloride resin (Aldrich, loading 1.73 mmol/g) swelled in DCM a solution of ethyl 3-[(trifluoroacetyl)amino]-4,5-dihydro-1H-pyrazolo[4,3-g]indolizine-8-carboxylate (1.5 eq) and TEA (2 eq) in DCM (10 ml 1 g) was added. The mixture was shaken for 24 hrs at room temperature. The resin was filtered off, washed with DMF (3×), DCM

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(3 \times), MeOH (3 \times), DCM, MeOH, DCM, MeOH, DCM (3 \times) and the unreacted chlorides were capped washing the resin with a solution of TEA/MeOH/DCM (1:2:7) (2 \times). Then the resin was washed with DCM (3 \times), MeOH (3 \times), DCM (3 \times) and dried under vacuum. Usually loading is over 90%: Calculated loading with increase of weight was 1.00 mmol/g The resin was then used in the next step.

The resin obtained from the first step was then treated with a solution of NaOH (40 eq), H₂O (1 ml/12 mmol NaOH), THF (2 ml/12 mmol NaOH) and minimal amount of MeOH to give a homogeneous solution.

The reaction was left shaking for 72 hrs at 50° C. Then was filtered off and washed sequentially with DMF (3 \times), MeON (3 \times), Water, MeOH, DCM, MeOH, DCM (3 \times).

After a check cleavage (40% TFA in DCM r.t. 30 min) the LCMS (HPLC Method 2) m/z 219 [M+H]⁺@ Rt 1.02 min (100% by ELS detection), the title compound was obtained.

Preparation 7

Preparation of Diethyl 1-(4-cyanobutyl)-1H-pyrrole-2,4-dicarboxylate (VII, Wherein n is 1 and Both of Ra' are —CH₂—CH₃)

To diethyl 1H-pyrrole-2,4-dicarboxylate (28 g, 0.13 mol) dissolved in ACN was added 30 g of potassium carbonate (0.21 mol) and 16.5 mL of 5-bromo-pentanenitrile (0.14 mol, d=1.377). The reaction was refluxed over night. The solvent was then evaporated under reduced pressure, the residue dissolved in ethyl acetate and washed 2 times with water. The crude was purified with a silica column (10 p silica) eluent cycloesane/ethyl acetate 7:3. 20 g of a white solid was obtained. HPLC (Method 2): m/z 293.51 [M+H]⁺@ Rt=5.61 min. 1H NMR (400 MHz, DMSO-d6) δ ppm 1.23-1.34 (m, 6 H), 1.42-1.56 (m, 2 H), 1.73-1.85 (m, 2 H), 3.27-3.28 (m, 2 H), 4.16-4.30 (m, 4 H), 4.36 (t, J=7.0 Hz, 2 H), 7.17 (d, J=2.0 Hz, 1 H), 7.83 (d, J=2.0 Hz, 1 H).

Preparation 8

Preparation of Ethyl 8-cyano-9-oxo-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2-carboxylate (VIII, Wherein n is 1 and Ra' is —CH₂—CH₃)

To the diethyl 1-(4-cyanobutyl)-1H-pyrrole-2,4-dicarboxylate (7 g) dissolved in anhydrous THF (150 mL), under nitrogen atmosphere, a solution of TertBuOK 1N in THF (50 mL) was added drop wise. The reaction was left stirring. After 15 minutes water and citric acid were added (pH=5), after 30 minutes of vigorous stirring the solution was extract with 100 mL of Ethyl acetate. The organic phase was then washed with water and NaHCO₃ (pH=10) dried on anhydrous Na₂SO₄. 5 g of a white solid were obtained (yield 87%). HPLC (Method 2): m/z 264 [M+NH₄]⁺@ Rt=4.6 min. 1H NMR (400 MHz, DMSO-d6) (mixture of tautomers cheto/enolic form ratio 55:45) ppm 1.35 (t, J=7.07 Hz, 3 H) 1.91-2.23 (m, 6 H) 2.35 (m, 2 H) 3.95 (t, J=6.83 Hz, 2 H 45%) 4.21 (q, J=7.07 Hz, 2 H 55%) 4.23 (q, J=7.07 Hz, 2 H 45%) 4.51 (dt, J=12.19 J=4.02 Hz, 2 H 55%) 4.57 (m, 1 H 55%) 7.12 (d, J=1.59 Hz, 1 H 45%) 7.17 (d, J=1.71, 1 H 55%) 7.31 (d, J=1.59, 1 H 45%) 7.70 (d, J=1.59, 1 H 55%) 10.82 (s, 1 H 45% OH enolic)

Example 3

Preparation of the Ethyl 3-amino-1,4,5,6-tetrahydropyrazolo[3,4-c]pyrrolo[1,2-a]azepine-9-carboxylate (I, Wherein n is 1, R1, R2 and R4 are Hydrogen, and R3 is —O—CH₂—CH₃)

To ethyl 8-cyano-9-oxo-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-2-carboxylate (12 g, 49 mmol) in ethanol a solu-

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tion of hydrazine monohydrate (6.5 g, 130 mmol) and acetic acid (9 g, 150 mmol) was added. The reaction was refluxed for 62 hours and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and NH₃. The organic phase was dried on Na₂SO₄. 10 g of a pale yellow solid were obtained (yield 78%).

HPLC(Method 2): m/z 261.3 [M+H]⁺@ Rt=3.13 min. 1H NMR (400 MHz, DMSO-d6) δ ppm 1.25 (t, J=7.1 Hz, 3 H) 2.54 (t, J=6.3 Hz, 2 H), 4.17 (q, J=7.2 Hz, 2 H), 4.10-4.23 (m, 2 H), 4.44 (br. s., 1 H), 6.82 (d, J=1.8 Hz, 1 H), 7.43 (d, J=2.0 Hz, 1 H), 11.70 (br. s., 1 H).

Example 4

Preparation of Compound Ethyl 3-[(trifluoroacetyl)amino]-1,4,5,6-tetrahydropyrazolo[3,4-c]pyrrolo[1,2-a]azepine-9-carboxylate (I, Wherein n is 1, R1 is —COCF₃, R2 and R4 are Hydrogen, and R3 is —O—CH₂—CH₃)

To the compound ethyl 3-amino-1,4,5,6-tetrahydropyrazolo[3,4-c]pyrrolo[1,2-a]azepine-9-carboxylate (5 g, 19.2 mmol) in DCM, was added TEA (11 g, 110 mmol) and TFAA (21 g 100 mmol). The reaction mixture was stirred at room temperature for 3 hours and then concentrated in vacuo. To the residue diluted NH₃ and MeOH were added and stirred for 1 hour. The solution was then concentrated. 100 mL of water was added and extracted with ethylacetate (3×100 mL). The organic phase was dried with anhydrous sodium sulphate to obtain a pale yellow solid (6.5 g, 92%). LCMS (HPLC Method 2): m/z 357 [M+H]⁺@ Rt 4.76 min (100% by ELS detection).

1H NMR (400 MHz, DMSO-D6) δ ppm 1.26 (t, J=7.1 Hz, 3 H) 1.94-2.05 (m, 2 H), 2.54-2.60 (m, 2 H), 4.16-4.21 (m, 2 H), 4.21-4.24 (m, 2 H), 7.02 (d, J=2.0 Hz, 1 H), 7.53 (d, J=1.8 Hz, 1 H), 11.27 (s, 1 H), 12.96 (br. s., 1 H).

Preparation 9

Preparation of Solid Supported 3-amino-1,4,5,6-tetrahydropyrazolo[3,4-c]pyrrolo[1,2-a]azepine-9-carboxylic acid (XVII, Wherein n is 1)

To polystyrene trityl chloride resin (Aldrich, loading 1.73 mmol/g) swelled in DCM a solution of ethyl 3-[(trifluoroacetyl)amino]-1,4,5,6-tetrahydropyrazolo[3,4-c]pyrrolo[1,2-a]azepine-9-carboxylate (1.5 eq) and TEA (2 eq) in DCM (10 mL/g) was added. The mixture was shaken for 24 hrs at room temperature. The resin was filtered off, washed with DMF (3 \times), DCM (3 \times), MeOH (3 \times), DCM, MeOH, DCM (3 \times) and the unreacted chlorides were capped washing the resin with a solution of TEA/MeOH/DCM (1:2:7) (2 \times). Then the resin was washed with DCM (3 \times), MeOH (3 \times), DCM (3 \times) and dried under vacuum. Usually loading is over 90%: Calculated loading with increase of weight was 1.00 mmol/g. The resin was then used in the next step.

The resin obtained from the first step was then treated with a solution of NaOH (40 eq), H₂O (1 ml/12 mmol NaOH), THF (2 ml/12 mmol NaOH) and minimal amount of MeOH to give a homogeneous solution.

The reaction was left shaking for 72 hrs at 50° C. Then was filtered off and washed sequentially with DMF (3 \times), MeOH (3 \times), Water, MeOH, DCM, MeOH, DCM (3 \times).

After a check cleavage (40% TFA in DCM room temperature for 30 min) the LCMS (HPLC Method 2) m/z 233 [M+H]⁺@ Rt 1.15 min (100% by ELS detection), the title compound was obtained.

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Example 6

Preparation A5-M1-B36 (entry 443, Table III)

To the 3-amino-4,5-dihydro-1H-pyrazolo[4,3-g]indolizine-8-carboxylic acid bond on resin (XVII, prepared as described under preparation 6), suspended in a solution of DCM/DMF 1:1 v/v, 1.5 eq of EDC, 1.5 eq of HOBT, 5 eq of TEA and 5 eq of allylamine were added. The suspension was left shaking for 24 hours at room temperature. The resin was filtered off, washed with DMF (3×), DCM (3×), MeOH (3×), DCM, MeOH, DCM, MeOH, DCM (3×). After cleavage (TFA/DCM 40%) the product was found in LCMS 90% pure.

To the resultant 3-amino-N-prop-2-en-1-yl-4,5-dihydro-1H-pyrazolo[4,3-g]indolizine-8-carboxamide bond resin (loading 1 mmol/g) (XVIII) suspended in DCM, 5 eq of 2-chloro-benzoyl chloride, and 5.1 eq. of Pyridine were added. The suspension was left shaking over night. The resin was filtered off, washed with DMF (3×), DCM (3×), MeOH (3×), DCM, MeOH, DCM, MeOH, DCM (3×). The resultant 3-[bis[(2-chlorophenyl)carbonyl]amino]-N-prop-2-en-1-yl-4,5-dihydro-1H-pyrazolo[4,3-g]indolizine-8-carboxamide obtained but not isolated (XIX), was suspended in a solution of NaOH 1N in DMF (1:4 v/v) and was left shaking over night at room temperature. Then washed with DMF (3×), MeOH (3×), water, MeOH, DCM, MeOH, DCM (3×). After cleavage (TFA/DCM 40%) the title product was recovered and analyzed.

LCMS (HPLC Method 1A) m/z 392 [M+H]+@ Rt 2.72 min (100% by UV:MS:CLND detection).

Example 7

Preparation A42-M2-B42 (entry 1187, Table III)

To the 3-amino-1,4,5,6-tetrahydropyrazolo[3,4-c]pyrrolo[1,2-a]azepine-9-carboxylic acid bond on resin (XVII, prepared as described under preparation 9), suspended in a solution of DCM/DMF 1:1 v/v, 1.5 eq of EDC, 1.5 eq of HOBT, 5 eq of TEA and 5 eq of piperidine were added. The suspension was left shaking for 24 hours at room temperature. The resin was filtered off, washed with DMF (3×), DCM (3×), MeOH (3×), DCM, MeOH, DCM, MeOH, DCM (3×). After a check cleavage (TFA/DCM 40%) the product was found in LCMS 90% pure.

To the resultant (3-amino-1,4,5,6-tetrahydropyrazolo[3,4-c]pyrrolo[1,2-a]azepin-9-yl)(piperidin-1-yl)methanone bond resin (loading 1 mmol/g) (XVIII) suspended in DCM, 5 eq of ethanesulphonyl chloride, and 5.1 eq. of Pyridine were added. The suspension was left shaking 24 hours at room temperature. The resin was filtered off, washed with DMF (3×), DCM (3×), MeOH (3×), DCM, MeOH, DCM, MeOH, DCM, MeOH, DCM (3×). A mixture of desiderate compound and the bis-sulphonil derivative was detected.

To the resultant mixture of compounds resin (loading 1 mmol/g) a solution of 0.1M TBAF in THF was added and was shaken for 35 hours at room temperature. after that time the resin was washed off with DMF 3×, MeOH, DMF, MeOH, DCM, MeOH, DCM 3×. After cleavage (TFA/DCM 40%) the title product was recovered and analyzed.

LCMS (HPLC Method 1A) m/z 396 [M+H]+@ Rt 2.68 min (100% by UV:MS:CLND detection).

Example 8

Preparation A47-M2-B27 (entry 1526, Table III)

To the 3-amino-1,4,5,6-tetrahydropyrazolo[3,4-c]pyrrolo[1,2-a]azepine-9-carboxylic acid bond on resin (XVII, pre-

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pared as described under preparation 9), suspended in a solution of DCM/DMF 1:1 v/v, 1.5 eq of EDC, 1.5 eq of HOBT, 5 eq of TEA and 5 eq of racemic butan-2-amine were added. The suspension was left shaking for 24 hours at room temperature. The resin was filtered off, washed with DMF (3×), DCM (3×), MeOH (3×), DCM, MeOH, DCM, MeOH, DCM (3×). After a check cleavage (TFA/DCM 40%) the product was found in LCMS 90% pure.

To the resultant 3-amino-N-(butan-2-yl)-1,4,5,6-tetrahydropyrazolo[3,4-c]pyrrolo[1,2-a]azepine-9-carboxamide bond resin (loading 1 mmol/g) (XVIII), swollen in DCM, was added TEA (10 eq), and 1-isocyanato-2-methoxybenzene (10 eq) and left shaking over night at room temperature. The resin was filtered off, washed with DMF (3×), DCM (3×), MeOH (3×), DCM, MeOH, DCM, MeOH, DCM (3×). After cleavage (TFA/DCM 40%) the title product was recovered and analyzed.

LCMS (HPLC Method 1A) m/z 437 [M+H]+@ Rt 3.42 min (100% by UV:MS:CLND detection).

Example 9

Preparation A1-M1-B1 (entry 1, Table III)

To the ethyl 3-amino-4,5-dihydro-1H-pyrazolo[4,3-g]indolizine-8-carboxylate (prepared as described under Example 1) dissolved in a solution of THF, 5 eq of TEA and later on 2.5 eq of benzoyl chloride were added. The suspension was left shaking for 6 hours at room temperature. A LCMS reveal a poli-acetylation. The solvent was evaporated and the residue was then diluted with water and extracted with EtOAc (2×). The combined organic layers were dried over Na₂SO₄, the solvent evaporated under vacuum and the product has not been isolated. To the poli-acetylated mixture obtained from the first step a solution 2N NaOH was add. The suspension was heated to 60° C. until a limpid solution was obtained. Ethyl ether was then added and the phase separated. HCl 2N was then added to the water solution until neutrality was reached. The formed precipitate and was separated and dried under vacuum. The 3-[(phenylcarbonyl)amino]-4,5-dihydro-1H-pyrazolo[4,3-g]indolizine-8-carboxylic acid was recovered.

LCMS (HPLC Method 2) m/z 323 [M+H]+@ Rt 1.35 min (100% by ELS detection). 1H NMR (DMSO-d₆, 400 MHz): δ ppm: 2.62 (t, J=6.7 Hz, 2 H), 4.13 (t, J=6.7 Hz, 2 H), 6.65 (d, J=1.2 Hz, 1 H), 7.31 (d, J=8.2 Hz, 2 H), 7.43 (d, J=1.7 Hz, 1 H), 7.59 (t, J=7.19 Hz, 1 H), 8.01 (d, J=8.6 Hz, 2 H), 10.51 (s, 1 H), 11.81 (br. s., 1 H) 12.88 (br. s., 1 H).

To the resultant carboxylic acid derived, 2 eq of EDC and 3 eq of HOBT.NH₄ were dissolved in DMF and left shaken over night at room temperature. Then water and EtOAc were added, the layer separated and the water was extracted with ethyl acetate a second time. The organic layer were combined, dried and evaporated under vacuum. The title compound was purified with preparative HPLC.

LCMS m/z 339 [M+NH₄]+@ Rt 2.87 min. 1H NMR (DMSO-d₆, 400 MHz): δ ppm: 1H NMR (DMSO-d₆, 400 MHz): δ ppm=2.86 (t, J=6.8 Hz, 2 H), 4.08 (t, J=6.7 Hz, 2 H), 6.69 (d, J=1.6 Hz, 1 H), 6.77 (br. s, 1H), 7.34 (br. s, 1H), 7.45 (d, J=1.5 Hz, 1 H), 7.51-7.57 (m, 2 H), 7.62 (t, J=7.3 Hz, 1 H), 8.02 (d, J=7.3 Hz, 2 H), 10.54 (s, 1 H).

Following the procedure described in examples 1 to 9 and by using any proper reactant as per the process of the invention, the following compounds of table III were also prepared.

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TABLE III

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
1	A1-M1-B1	2	2.87	322	
2	A2-M1-B1	2	2.97	336	
3	A3-M1-B1	2	2.18	286	
4	A1-M1-B2	2	2.45	407	
5	A1-M1-B3	1A	1.91	405	
6	A1-M1-B4	2	4.08	426	
7	A1-M1-B5	2	3.98	404	
8	A1-M1-B6	1A	2.54	350	
9	A4-M1-B7	1A	2.52	372	
10	A5-M1-B8	1A	2.85	410	
11	A6-M1-B9	2	4.28	432	
12	A7-M1-B10	2	3.63	384	
13	A8-M1-B11	1B	6.6	452	
14	A9-M1-B11	1B	6.1	424	
15	A10-M1-B11	1B	7.13	454	
16	A11-M1-B11	1B	6.43	478	
17	A12-M1-B11	1B	6.43	478	
18	A13-M1-B11	1B	6.7	428	
19	A14-M1-B12	1B	5.62	440	
20	A15-M1-B12	1B	5.7	454	
21	A12-M1-B12	1B	5.34	470	
22	A13-M1-B12	1B	5.63	420	
23	A14-M1-B13	1B	6.19	474	
24	A15-M1-B13	1B	6.26	488	
25	A8-M1-B13	1B	6.09	478	
26	A9-M1-B13	1B	5.53	450	
27	A15-M1-B11	1B	6.74	462	
28	A8-M1-B12	1B	5.49	444	
29	A9-M1-B12	1B	4.84	416	
30	A10-M1-B12	1B	6.24	446	
31	A11-M1-B12	1B	5.29	470	
32	A10-M1-B13	1B	6.71	480	
33	A11-M1-B13	1B	5.9	504	
34	A12-M1-B13	1B	5.94	504	
35	A13-M1-B13	1B	6.22	454	
36	A14-M1-B14	1B	3.31	447	
37	A15-M1-B14	1B	3.3	461	
38	A8-M1-B14	1B	3.12	451	
39	A9-M1-B14	1B	2.65	423	
40	A10-M1-B14	1B	3.86	453	
41	A11-M1-B14	1B	3.02	477	
42	A12-M1-B14	1B	3.06	477	
43	A13-M1-B14	1B	3.18	427	
44	A14-M1-B15	1B	5.55	456	
45	A15-M1-B15	1B	5.62	470	
46	A8-M1-B15	1B	5.42	460	
47	A9-M1-B15	1B	4.75	432	
48	A10-M1-B15	1B	6.15	462	
49	A11-M1-B15	1B	5.21	486	
50	A12-M1-B15	1B	5.26	486	
51	A13-M1-B15	1B	5.55	436	
52	A14-M1-B16	1B	5.28	432	
53	A15-M1-B16	1B	5.35	446	
54	A8-M1-B16	1B	5.13	436	
55	A13-M1-B16	1B	5.26	412	
56	A9-M1-B16	1B	4.41	408	
57	A10-M1-B16	1B	5.94	438	
58	A11-M1-B16	1B	4.93	462	
59	A12-M1-B16	1B	4.97	462	
60	A14-M1-B11	1B	6.67	448	
61	A16-M1-B10	2	2.52	462	
62	A16-M1-B17	2	2.82	476	
63	A16-M1-B18	2	2	434	
64	A16-M1-B19	2	2.3	448	
65	A1-M1-B20	2	4.35	404	
66	A1-M1-B21	2	4.53	472	
67	A1-M1-B22	2	3.92	442	
68	A1-M1-B23	2	4.9	438	
69	A17-M1-B24	1A	2.08	449	
70	A18-M1-B24	1A	2.39	453	
71	A3-M1-B24	1A	1.67	383	
72	A19-M1-B24	1A	2.5	447	
73	A20-M1-B24	1A	1.96	437	
74	A11-M1-B24	1A	1.96	463	
75	A21-M1-B24	1A	2.04	433	
76	A22-M1-B24	1A	2.03	449	
77	A4-M1-B24	1A	1.92	399	

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TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺
5	A6-M1-B24	1A	2.17	449
	A23-M1-B24	1A	1.52	387
	A24-M1-B24	1A	2.58	447
	A25-M1-B24	1A	2.86	461
	A26-M1-B24	1A	2.26	455
	A27-M1-B24	1A	1.7	385
10	A28-M1-B24	1A	2.07	437
	A29-M1-B24	1A	1.46	357
	A8-M1-B24	1A	2.08	437
	A30-M1-B24	1A	2.37	451
	A17-M1-B25	1A	2.18	443
	A31-M1-B25	1A	2.06	456
15	A18-M1-B25	1A	2.51	447
	A3-M1-B25	1A	1.75	377
	A19-M1-B25	1A	2.58	441
	A20-M1-B25	1A	2.07	431
	A32-M1-B25	1A	1.67	414
20	A11-M1-B25	1A	2.08	457
	A21-M1-B25	1A	2.14	427
	A24-M1-B25	1A	2.67	441
	A26-M1-B25	1A	2.37	449
	A33-M1-B25	1A	1.95	393
25	A5-M1-B25	1A	2.12	447
	A29-M1-B25	1A	1.52	351
	A1-M1-B25	1A	2.07	413
	A8-M1-B25	1A	2.2	431
	A17-M1-B26	1A	2.32	443
	A31-M1-B26	1A	2.19	456
	A11-M1-B26	1A	2.65	447
30	A3-M1-B26	1A	1.87	377
	A19-M1-B26	1A	2.73	441
	A20-M1-B26	1A	2.19	431
	A32-M1-B26	1A	1.78	414
	A11-M1-B26	1A	2.2	457
	A21-M1-B26	1A	2.29	427
35	A22-M1-B26	1A	2.29	443
	A6-M1-B26	1A	2.4	443
	A24-M1-B26	1A	2.83	441
	A26-M1-B26	1A	2.55	449
	A33-M1-B26	1A	2.09	393
	A5-M1-B26	1A	2.25	447
40	A34-M1-B26	1A	1.76	365
	A27-M1-B26	1A	1.91	379
	A28-M1-B26	1A	2.33	431
	A1-M1-B26	1A	2.18	413
	A8-M1-B26	1A	2.35	431
	A17-M1-B27	1A	3.01	408
	A31-M1-B27	1A	2.89	421
	A18-M1-B27	1A	3.37	412
	A3-M1-B27	1A	2.6	342
	A19-M1-B27	1A	3.39	406
	A20-M1-B27	1A	2.92	396
	A32-M1-B27	1A	2.43	379
	A21-M1-B27	1A	3.03	392
	A6-M1-B27	1A	3.1	408
	A23-M1-B27	1A	2.34	346
	A24-M1-B27	1A	3.46	406
	A25-M1-B27	1A	3.69	420
	A26-M1-B27	1A	3.27	414
	A35-M1-B27	1A	3.32	406
	A33-M1-B27	1A	2.83	358
55	A5-M1-B27	1A	2.99	412
	A28-M1-B27	1A	3.06	396
	A1-M1-B27	1A	2.92	378
	A8-M1-B27	1A	3.08	396
	A30-M1-B27	1A	3.36	410
	A17-M1-B28	1A	3.11	420
60	A31-M1-B28	1A	3.02	433
	A18-M1-B28	1A	3.45	424
	A1-M1-B27	1A	2.92	378
	A8-M1-B27	1A	3.08	396
	A3-M1-B28	1A	2.73	354
	A19-M1-B28	1A	3.48	418
	A20-M1-B28	1A	3.04	408
	A32-M1-B28	1A	2.58	391
	A11-M1-B28	1A	3.04	434
65	A21-M1-B28	1A	3.14	404

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
155	A4-M1-B28	1A	3.08	370	5
156	A6-M1-B28	1A	3.21	420	
157	A23-M1-B28	1A	2.48	358	
158	A24-M1-B28	1A	3.55	418	
159	A26-M1-B28	1A	3.37	426	
160	A35-M1-B28	1A	3.4	418	
161	A36-M1-B28	1A	3.15	438	10
162	A33-M1-B28	1A	2.94	370	
163	A5-M1-B28	1A	3.1	424	
164	A28-M1-B28	1A	3.16	408	
165	A29-M1-B28	1A	2.44	328	
166	A1-M1-B28	1A	3.03	390	
167	A8-M1-B28	1A	3.19	408	
168	A30-M1-B28	1A	3.46	422	15
169	A17-M1-B29	1A	2.12	423	
170	A18-M1-B29	1A	2.44	427	
171	A3-M1-B29	1A	1.69	357	
172	A20-M1-B29	1A	2.01	411	
173	A32-M1-B29	1A	1.63	394	20
174	A11-M1-B29	1A	2.03	437	
175	A21-M1-B29	1A	2.07	407	
176	A22-M1-B29	1A	2.1	423	
177	A4-M1-B29	1A	1.98	373	
178	A6-M1-B29	1A	2.23	423	
179	A24-M1-B29	1A	2.62	421	
180	A26-M1-B29	1A	2.32	429	25
181	A33-M1-B29	1A	1.91	373	
182	A27-M1-B29	1A	1.75	359	
183	A28-M1-B29	1A	2.13	411	
184	A1-M1-B29	1A	2	393	
185	A8-M1-B29	1A	2.13	411	
186	A17-M1-B8	1A	2.87	406	30
187	A18-M1-B8	1A	3.24	410	
188	A3-M1-B8	1A	2.44	340	
189	A19-M1-B8	1A	3.27	404	
190	A20-M1-B8	1A	2.79	394	
191	A32-M1-B8	1A	2.3	377	
192	A11-M1-B8	1A	2.79	420	35
193	A21-M1-B8	1A	2.88	390	
194	A22-M1-B8	1A	2.85	406	
195	A4-M1-B8	1A	2.79	356	
196	A6-M1-B8	1A	2.97	406	
197	A24-M1-B8	1A	3.35	404	
198	A25-M1-B8	1A	3.57	418	40
199	A26-M1-B8	1A	3.14	412	
200	A35-M1-B8	1A	3.17	404	
201	A36-M1-B8	1A	2.92	424	
202	A33-M1-B8	1A	2.68	356	
203	A34-M1-B8	1A	2.32	328	
204	A27-M1-B8	1A	2.51	342	
205	A28-M1-B8	1A	2.93	394	45
206	A8-M1-B8	1A	2.95	394	
207	A30-M1-B8	1A	3.23	408	
208	A17-M1-B10	1A	2.82	394	
209	A31-M1-B10	1A	2.67	407	
210	A18-M1-B10	1A	3.18	398	
211	A3-M1-B10	1A	2.37	328	50
212	A19-M1-B10	1A	3.23	392	
213	A20-M1-B10	1A	2.72	382	
214	A32-M1-B10	1A	2.22	365	
215	A11-M1-B10	1A	2.73	408	
216	A22-M1-B10	1A	2.78	394	
217	A6-M1-B10	1A	2.92	394	55
218	A24-M1-B10	1A	3.31	392	
219	A25-M1-B10	1A	3.55	406	
220	A26-M1-B10	1A	3.08	400	
221	A35-M1-B10	1A	3.13	392	
222	A36-M1-B10	1A	2.86	412	
223	A33-M1-B10	1A	2.6	344	60
224	A5-M1-B10	1A	2.78	398	
225	A27-M1-B10	1A	2.44	330	
226	A28-M1-B10	1A	2.87	382	
227	A1-M1-B10	1A	2.71	364	
228	A8-M1-B10	1A	2.88	382	
229	A30-M1-B10	1A	3.17	396	65
230	A17-M1-B17	1A	3.07	408	
231	A31-M1-B17	1A	2.95	421	

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺
232	A18-M1-B17	1A	3.41	412
233	A3-M1-B17	1A	2.65	342
234	A19-M1-B17	1A	3.43	406
235	A20-M1-B17	1A	2.97	396
236	A32-M1-B17	1A	2.5	379
237	A11-M1-B17	1A	2.97	422
238	A21-M1-B17	1A	3.07	392
239	A4-M1-B17	1A	2.98	358
240	A6-M1-B17	1A	3.15	408
241	A24-M1-B17	1A	3.5	406
242	A25-M1-B17	1A	3.72	420
243	A26-M1-B17	1A	3.33	414
244	A36-M1-B17	1A	3.1	426
245	A33-M1-B17	1A	2.88	358
246	A5-M1-B17	1A	3.04	412
247	A27-M1-B17	1A	2.7	344
248	A28-M1-B17	1A	3.11	396
249	A1-M1-B17	1A	2.96	378
250	A8-M1-B17	1A	3.13	396
251	A30-M1-B17	1A	3.4	410
252	A17-M1-B30	1A	2.7	392
253	A31-M1-B30	1A	2.52	405
254	A19-M1-B30	1A	3.11	390
255	A20-M1-B30	1A	2.58	380
256	A32-M1-B30	1A	2.08	363
257	A21-M1-B30	1A	2.68	376
258	A22-M1-B30	1A	2.65	392
259	A4-M1-B30	1A	2.58	342
260	A24-M1-B30	1A	3.19	390
261	A25-M1-B30	1A	3.45	404
262	A26-M1-B30	1A	2.96	398
263	A35-M1-B30	1A	3.01	390
264	A36-M1-B30	1A	2.72	410
265	A33-M1-B30	1A	2.46	342
266	A5-M1-B30	1A	2.65	396
267	A28-M1-B30	1A	2.73	380
268	A1-M1-B30	1A	2.57	362
269	A8-M1-B30	1A	2.74	380
270	A30-M1-B30	1A	3.06	394
271	A17-M1-B3	1A	2.04	435
272	A31-M1-B3	1A	1.93	448
273	A18-M1-B3	1A	2.38	439
274	A3-M1-B3	1A	1.62	369
275	A37-M1-B3	1A	2.14	448
276	A19-M1-B3	1A	2.47	433
277	A20-M1-B3	1A	1.92	423
278	A32-M1-B3	1A	1.55	406
279	A11-M1-B3	1A	1.94	449
280	A21-M1-B3	1A	2.01	419
281	A22-M1-B3	1A	2	435
282	A4-M1-B3	1A	1.88	385
283	A6-M1-B3	1A	2.13	435
284	A24-M1-B3	1A	2.55	433
285	A25-M1-B3	1A	2.85	447
286	A26-M1-B3	1A	2.23	441
287	A36-M1-B3	1A	2.07	453
288	A34-M1-B3	1A	1.53	357
289	A27-M1-B3	1A	1.65	371
290	A28-M1-B3	1A	2.04	423
291	A29-M1-B3	1A	1.41	343
292	A8-M1-B3	1A	2.05	423
293	A30-M1-B3	1A	2.39	437
294	A17-M1-B7	1A	2.63	422
295	A31-M1-B7	1A	2.46	435
296	A3-M1-B7	1A	2.17	356
297	A19-M1-B7	1A	3.06	420
298	A20-M1-B7	1A	2.52	410
299	A32-M1-B7	1A	2.04	393
300	A11-M1-B7	1A	2.54	436
301	A21-M1-B7	1A	2.62	406
302	A22-M1-B7	1A	2.6	422
303	A6-M1-B7	1A	2.74	422
304	A24-M1-B7	1A	3.13	420
305	A25-M1-B7	1A	3.39	434
306	A26-M1-B7	1A	2.89	428
307	A35-M1-B7	1A	2.95	420
308	A36-M1-B7	1A	2.67	440

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
309	A33-M1-B7	1A	2.42	372	5
310	A5-M1-B7	1A	2.58	426	
311	A34-M1-B7	1A	2.06	344	
312	A27-M1-B7	1A	2.23	358	
313	A28-M1-B7	1A	2.68	410	
314	A29-M1-B7	1A	1.89	330	
315	A8-M1-B7	1A	2.69	410	10
316	A30-M1-B7	1A	3	424	
317	A17-M1-B31	1A	2.24	463	
318	A31-M1-B31	1A	2.13	476	
319	A18-M1-B31	1A	2.51	467	
320	A3-M1-B31	1A	1.84	397	
321	A19-M1-B31	1A	2.63	461	15
322	A20-M1-B31	1A	2.11	451	
323	A32-M1-B31	1A	1.76	434	
324	A11-M1-B31	1A	2.14	477	
325	A21-M1-B31	1A	2.22	447	
326	A22-M1-B31	1A	2.2	463	
327	A4-M1-B31	1A	2.11	413	20
328	A24-M1-B31	1A	2.71	461	
329	A26-M1-B31	1A	2.43	469	
330	A33-M1-B31	1A	2.04	413	
331	A5-M1-B31	1A	2.17	467	
332	A27-M1-B31	1A	1.88	399	
333	A28-M1-B31	1A	2.26	451	
334	A29-M1-B31	1A	1.62	371	25
335	A1-M1-B31	1A	2.13	433	
336	A8-M1-B31	1A	2.26	451	
337	A17-M1-B32	1A	2.11	463	
338	A31-M1-B32	1A	2	476	
339	A18-M1-B32	1A	2.41	467	
340	A37-M1-B32	1A	2.21	476	30
341	A19-M1-B32	1A	2.52	461	
342	A20-M1-B32	1A	2	451	
343	A32-M1-B32	1A	1.63	434	
344	A11-M1-B32	1A	2.03	477	
345	A21-M1-B32	1A	2.09	447	
346	A4-M1-B32	1A	1.98	413	35
347	A6-M1-B32	1A	2.2	463	
348	A24-M1-B32	1A	2.6	461	
349	A25-M1-B32	1A	2.88	475	
350	A26-M1-B32	1A	2.3	469	
351	A35-M1-B32	1A	2.4	461	
352	A36-M1-B32	1A	2.13	481	40
353	A33-M1-B32	1A	1.89	413	
354	A5-M1-B32	1A	2.02	467	
355	A27-M1-B32	1A	1.75	399	
356	A28-M1-B32	1A	2.12	451	
357	A1-M1-B32	1A	2	433	
358	A8-M1-B32	1A	2.12	451	
359	A30-M1-B32	1A	2.44	465	45
360	A17-M1-B33	1A	2.62	410	
361	A31-M1-B33	1A	2.44	423	
362	A3-M1-B33	1A	2.15	344	
363	A19-M1-B33	1A	3.05	408	
364	A20-M1-B33	1A	2.51	398	
365	A32-M1-B33	1A	2.01	381	50
366	A11-M1-B33	1A	2.51	424	
367	A21-M1-B33	1A	2.61	394	
368	A22-M1-B33	1A	2.59	410	
369	A4-M1-B33	1A	2.5	360	
370	A24-M1-B33	1A	3.13	408	
371	A25-M1-B33	1A	3.39	422	55
372	A26-M1-B33	1A	2.89	416	
373	A35-M1-B33	1A	2.93	408	
374	A36-M1-B33	1A	2.65	428	
375	A33-M1-B33	1A	2.39	360	
376	A5-M1-B33	1A	2.57	414	
377	A27-M1-B33	1A	2.22	346	
378	A28-M1-B33	1A	2.66	398	60
379	A1-M1-B33	1A	2.5	380	
380	A8-M1-B33	1A	2.67	398	
381	A30-M1-B33	1A	3	412	
382	A17-M1-B34	1A	2.16	503	
383	A31-M1-B34	1A	2.05	516	
384	A18-M1-B34	1A	2.48	507	65
385	A3-M1-B34	1A	1.77	437	

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺
386	A19-M1-B34	1A	2.57	501
387	A20-M1-B34	1A	2.05	491
388	A32-M1-B34	1A	1.7	474
389	A11-M1-B34	1A	2.08	517
390	A21-M1-B34	1A	2.14	487
391	A22-M1-B34	1A	2.14	503
392	A4-M1-B34	1A	2.04	453
393	A6-M1-B34	1A	2.26	503
394	A24-M1-B34	1A	2.63	501
395	A25-M1-B34	1A	2.9	515
396	A26-M1-B34	1A	2.36	509
397	A35-M1-B34	1A	2.44	501
398	A36-M1-B34	1A	2.19	521
399	A33-M1-B34	1A	1.95	453
400	A5-M1-B34	1A	2.11	507
401	A27-M1-B34	1A	1.81	439
402	A28-M1-B34	1A	2.18	491
403	A29-M1-B34	1A	1.57	411
404	A8-M1-B34	1A	2.15	491
405	A30-M1-B34	1A	2.49	505
406	A17-M1-B35	1A	2.29	498
407	A31-M1-B35	1A	2.18	511
408	A18-M1-B35	1A	2.6	502
409	A37-M1-B35	1A	2.38	511
410	A19-M1-B35	1A	2.65	496
411	A32-M1-B35	1A	1.83	469
412	A11-M1-B35	1A	2.19	512
413	A22-M1-B35	1A	2.25	498
414	A4-M1-B35	1A	2.17	448
415	A6-M1-B35	1A	2.38	498
416	A25-M1-B35	1A	3.01	510
417	A26-M1-B35	1A	2.48	504
418	A35-M1-B35	1A	2.55	496
419	A36-M1-B35	1A	2.32	516
420	A5-M1-B35	1A	2.24	502
421	A27-M1-B35	1A	1.94	434
422	A28-M1-B35	1A	2.31	486
423	A29-M1-B35	1A	1.69	406
424	A1-M1-B35	1A	2.18	468
425	A8-M1-B35	1A	2.31	486
426	A30-M1-B35	1A	2.63	500
427	A17-M1-B36	1A	2.76	392
428	A31-M1-B36	1A	2.6	405
429	A18-M1-B36	1A	3.13	396
430	A3-M1-B36	1A	2.29	326
431	A19-M1-B36	1A	3.17	390
432	A32-M1-B36	1A	2.15	363
433	A11-M1-B36	1A	2.66	406
434	A21-M1-B36	1A	2.77	376
435	A22-M1-B36	1A	2.73	392
436	A6-M1-B36	1A	2.85	392
437	A24-M1-B36	1A	3.26	390
438	A25-M1-B36	1A	3.5	404
439	A26-M1-B36	1A	3.03	398
440	A35-M1-B36	1A	3.08	390
441	A36-M1-B36	1A	2.8	410
442	A33-M1-B36	1A	2.54	342
443	A5-M1-B36	1A	2.72	396
444	A34-M1-B36	1A	2.17	314
445	A27-M1-B36	1A	2.35	328
446	A28-M1-B36	1A	2.81	380
447	A1-M1-B36	1A	2.64	362
448	A8-M1-B36	1A	2.81	380
449	A30-M1-B36	1A	3.13	394
450	A17-M1-B37	1A	2.05	449
451	A31-M1-B37	1A	1.94	462
452	A18-M1-B37	1A	2.35	453
453	A3-M1-B37	1A	1.64	383
454	A19-M1-B37	1A	2.43	447
455	A20-M1-B37	1A	1.93	437
456	A32-M1-B37	1A	1.57	420
457	A11-M1-B37	1A	1.96	463
458	A21-M1-B37	1A	2.02	433
459	A22-M1-B37	1A	2.04	449
460	A4-M1-B37	1A	1.9	399
461	A6-M1-B37	1A	2.14	449
462	A24-M1-B37	1A	2.56	447

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
463	A25-M1-B37	1A	2.78	461	
464	A26-M1-B37	1A	2.24	455	
465	A36-M1-B37	1A	2.05	467	
466	A33-M1-B37	1A	1.84	399	
467	A5-M1-B37	1A	1.98	453	
468	A27-M1-B37	1A	1.68	385	
469	A28-M1-B37	1A	2.05	437	5
470	A29-M1-B37	1A	1.45	357	
471	A8-M1-B37	1A	2.05	437	
472	A30-M1-B37	1A	2.37	451	
473	A17-M1-B38	1A	2.97	438	
474	A31-M1-B38	1A	2.85	451	
475	A3-M1-B38	1A	2.56	372	
476	A19-M1-B38	1A	3.37	436	10
477	A20-M1-B38	1A	2.88	426	
478	A32-M1-B38	1A	2.4	409	
479	A11-M1-B38	1A	2.88	452	
480	A21-M1-B38	1A	2.98	422	
481	A22-M1-B38	1A	2.95	438	
482	A4-M1-B38	1A	2.9	388	20
483	A6-M1-B38	1A	3.07	438	
484	A24-M1-B38	1A	3.44	436	
485	A25-M1-B38	1A	3.66	450	
486	A26-M1-B38	1A	3.24	444	
487	A35-M1-B38	1A	3.27	436	
488	A36-M1-B38	1A	3.02	456	25
489	A5-M1-B38	1A	2.95	442	
490	A27-M1-B38	1A	2.62	374	
491	A28-M1-B38	1A	3.03	426	
492	A1-M1-B38	1A	2.88	408	
493	A8-M1-B38	1A	3.05	426	
494	A30-M1-B38	1A	3.33	440	30
495	A17-M1-B39	1A	3.09	408	
496	A31-M1-B39	1A	2.99	421	
497	A3-M1-B39	1A	2.7	342	
498	A19-M1-B39	1A	3.46	406	
499	A20-M1-B39	1A	3	396	
500	A32-M1-B39	1A	2.53	379	35
501	A11-M1-B39	1A	3.01	422	
502	A21-M1-B39	1A	3.11	392	
503	A22-M1-B39	1A	3.06	408	
504	A4-M1-B39	1A	3.04	358	
505	A6-M1-B39	1A	3.19	408	
506	A24-M1-B39	1A	3.54	406	
507	A25-M1-B39	1A	3.75	420	40
508	A26-M1-B39	1A	3.36	414	
509	A35-M1-B39	1A	3.38	406	
510	A36-M1-B39	1A	3.13	426	
511	A33-M1-B39	1A	2.92	358	
512	A5-M1-B39	1A	3.07	412	
513	A34-M1-B39	1A	2.57	330	45
514	A27-M1-B39	1A	2.75	344	
515	A28-M1-B39	1A	3.15	396	
516	A1-M1-B39	1A	3	378	
517	A8-M1-B39	1A	3.16	396	
518	A30-M1-B39	1A	3.43	410	
519	A17-M1-B40	1A	2.09	463	50
520	A31-M1-B40	1A	1.97	476	
521	A3-M1-B40	1A	1.68	397	
522	A19-M1-B40	1A	2.49	461	
523	A20-M1-B40	1A	1.96	451	
524	A32-M1-B40	1A	1.62	434	
525	A11-M1-B40	1A	2	477	55
526	A21-M1-B40	1A	2.07	447	
527	A22-M1-B40	1A	2.07	463	
528	A4-M1-B40	1A	1.94	413	
529	A6-M1-B40	1A	2.18	463	
530	A24-M1-B40	1A	2.57	461	
531	A25-M1-B40	1A	2.85	475	60
532	A26-M1-B40	1A	2.29	469	
533	A35-M1-B40	1A	2.37	461	
534	A36-M1-B40	1A	2.12	481	
535	A33-M1-B40	1A	1.87	413	
536	A5-M1-B40	1A	2.02	467	
537	A34-M1-B40	1A	1.6	385	65
538	A27-M1-B40	1A	1.73	399	
539	A28-M1-B40	1A	2.1	451	

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
540	A29-M1-B40	1A	1.49	371	
541	A1-M1-B40	1A	1.97	433	
542	A8-M1-B40	1A	2.11	451	
543	A30-M1-B40	1A	2.42	465	
544	A17-M1-B41	1A	2.92	406	
545	A31-M1-B41	1A	2.78	419	
546	A18-M1-B41	1A	3.28	410	5
547	A3-M1-B41	1A	2.49	340	
548	A19-M1-B41	1A	3.31	404	
549	A20-M1-B41	1A	2.83	394	
550	A32-M1-B41	1A	2.33	377	
551	A11-M1-B41	1A	2.82	420	
552	A21-M1-B41	1A	2.93	390	
553	A22-M1-B41	1A	2.88	406	
554	A4-M1-B41	1A	2.85	356	10
555	A6-M1-B41	1A	3.02	406	
556	A24-M1-B41	1A	3.39	404	
557	A25-M1-B41	1A	3.61	418	
558	A26-M1-B41	1A	3.19	412	
559	A35-M1-B41	1A	3.22	404	20
560	A33-M1-B41	1A	2.72	356	
561	A5-M1-B41	1A	2.89	410	
562	A27-M1-B41	1A	2.56	342	
563	A28-M1-B41	1A	2.98	394	
564	A1-M1-B41	1A	2.82	376	
565	A30-M1-B41	1A	3.27	408	25
566	A17-M1-B42	1A	3.14	420	
567	A18-M1-B42	1A	3.5	424	
568	A19-M1-B42	1A	3.51	418	
569	A32-M1-B42	1A	2.6	391	
570	A11-M1-B42	1A	3.06	434	
571	A22-M1-B42	1A	3.11	420	30
572	A4-M1-B42	1A	3.09	370	
573	A24-M1-B42	1A	3.58	418	
574	A25-M1-B42	1A	3.79	432	
575	A26-M1-B42	1A	3.41	426	
576	A35-M1-B42	1A	3.43	418	
577	A36-M1-B42	1A	3.18	438	35
578	A5-M1-B42	1A	3.12	424	
579	A34-M1-B42	1A	2.63	342	
580	A27-M1-B42	1A	2.81	356	
581	A28-M1-B42	1A	3.21	408	
582	A1-M1-B42	1A	3.06	390	
583	A8-M1-B42	1A	3.22	408	
584	A30-M1-B42	1A	3.48	422	40
585	A17-M1-B6	1A	2.66	380	
586	A31-M1-B6	1A	2.49	393	
587	A18-M1-B6	1A	3.04	384	
588	A3-M1-B6	1A	2.19	314	
589	A19-M1-B6	1A	3.09	378	
590	A20-M1-B6	1A	2.55	368	45
591	A32-M1-B6	1A	2.04	351	
592	A11-M1-B6	1A	2.55	394	
593	A6-M1-B6	1A	2.76	380	
594	A24-M1-B6	1A	3.17	378	
595	A25-M1-B6	1A	3.43	392	
596	A26-M1-B6	1A	2.92	386	50
597	A35-M1-B6	1A	2.98	378	
598	A36-M1-B6	1A	2.69	398	
599	A33-M1-B6	1A	2.42	330	
600	A5-M1-B6	1A	2.62	384	
601	A28-M1-B6	1A	2.7	368	
602	A8-M1-B6	1A	2.71	368	
603	A30-M1-B6	1A	3.04	382	55
604	A17-M1-B43	1A	2.16	449	
605	A18-M1-B43	1A	2.47	453	
606	A19-M1-B43	1A	2.58	447	
607	A32-M1-B43	1A	1.68	420	60
608	A11-M1-B43	1A	2.05	463	
609	A21-M1-B43	1A	2.13	433	
610	A22-M1-B43	1A	2.14	449	
611	A6-M1-B43	1A	2.26	449	
612	A24-M1-B43	1A	2.65	447	
613	A26-M1-B43	1A	2.35	455	
614	A33-M1-B43	1A	1.94	399	65
615	A5-M1-B43	1A	2.1	453	
616	A28-M1-B43	1A	2.18	437	

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
617	A1-M1-B43	1A	2.05	419	
618	A8-M1-B43	1A	2.17	437	
619	A38-M1-B41	3	4.82	444	
620	A39-M1-B8	3	5.21	418	
621	A39-M1-B34	3	4.52	515	
622	A14-M2-B11	2	6.05	462	
623	A15-M2-B11	2	5.97	476	5
624	A8-M2-B11	2	6	466	
625	A9-M2-B11	2	5.27	438	
626	A14-M2-B12	2	5.03	454	
627	A15-M2-B12	2	4.93	468	
628	A9-M2-B12	2	4.27	430	
629	A16-M2-B12	2	3.45	538	
630	A9-M2-B13	2	4.67	464	
631	A14-M2-B15	2	4.9	470	
632	A8-M2-B15	2	4.77	474	
633	A9-M2-B15	2	4.18	446	
634	A16-M2-B15	2	3.4	554	
635	A14-M2-B19	2	3.93	378	
636	A8-M2-B19	2	3.87	382	15
637	A9-M2-B19	2	3.08	354	
638	A16-M2-B19	2	2.53	462	
639	A26-M2-B43	1A	2.43	469	
640	A17-M2-B24	1A	2.145	463	
641	A19-M2-B24	1A	2.55	461	
642	A32-M2-B24	1A	1.635	434	25
643	A11-M2-B24	1A	2.045	477	
644	A4-M2-B24	1A	1.99	413	
645	A6-M2-B24	1A	2.25	463	
646	A24-M2-B24	1A	2.615	461	
647	A25-M2-B24	1A	2.91	475	
648	A28-M2-B24	1A	2.18	451	30
649	A29-M2-B24	1A	1.505	371	
650	A8-M2-B24	1A	2.18	451	
651	A30-M2-B24	1A	2.495	465	
652	A17-M2-B25	1A	2.24	457	
653	A18-M2-B25	1A	2.59	461	
654	A3-M2-B25	1A	1.82	391	35
655	A19-M2-B25	1A	2.67	455	
656	A20-M2-B25	1A	2.14	445	
657	A32-M2-B25	1A	1.725	428	
658	A21-M2-B25	1A	2.21	441	
659	A4-M2-B25	1A	2.11	407	
660	A6-M2-B25	1A	2.34	457	
661	A26-M2-B25	1A	2.48	463	40
662	A33-M2-B25	1A	2.04	407	
663	A34-M2-B25	1A	1.715	379	
664	A28-M2-B25	1A	2.265	445	
665	A1-M2-B25	1A	2.13	427	
666	A8-M2-B25	1A	2.27	445	
667	A17-M2-B26	1A	2.4	457	45
668	A31-M2-B26	1A	2.285	470	
669	A18-M2-B26	1A	2.76	461	
670	A3-M2-B26	1A	1.95	391	
671	A19-M2-B26	1A	2.84	455	
672	A20-M2-B26	1A	2.31	445	
673	A32-M2-B26	1A	1.855	428	50
674	A11-M2-B26	1A	2.31	471	
675	A21-M2-B26	1A	2.39	441	
676	A6-M2-B26	1A	2.51	457	
677	A24-M2-B26	1A	2.905	455	
678	A26-M2-B26	1A	2.645	463	
679	A33-M2-B26	1A	2.18	407	55
680	A5-M2-B26	1A	2.36	461	
681	A28-M2-B26	1A	2.44	445	
682	A1-M2-B26	1A	2.285	427	
683	A8-M2-B26	1A	2.445	445	
684	A17-M2-B27	1A	3.09	422	
685	A31-M2-B27	1A	2.96	435	
686	A18-M2-B27	1A	3.42	426	60
687	A19-M2-B27	1A	3.45	420	
688	A20-M2-B27	1A	3.02	410	
689	A32-M2-B27	1A	2.51	393	
690	A11-M2-B27	1A	2.99	436	
691	A22-M2-B27	1A	3.05	422	65
692	A6-M2-B27	1A	3.17	422	
693	A24-M2-B27	1A	3.53	420	

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
694	A25-M2-B27	1A	3.75	434	
695	A26-M2-B27	1A	3.35	428	
696	A35-M2-B27	1A	3.37	420	
697	A36-M2-B27	1A	3.11	440	
698	A5-M2-B27	1A	3.08	426	
699	A27-M2-B27	1A	2.73	358	
700	A28-M2-B27	1A	3.14	410	5
701	A1-M2-B27	1A	2.99	392	
702	A8-M2-B27	1A	3.15	410	
703	A30-M2-B27	1A	3.41	424	
704	A17-M2-B28	1A	3.18	434	
705	A31-M2-B28	1A	3.085	447	
706	A18-M2-B28	1A	3.52	438	
707	A19-M2-B28	1A	3.54	432	
708	A20-M2-B28	1A	3.13	422	
709	A32-M2-B28	1A	2.63	405	
710	A11-M2-B28	1A	3.1	448	
711	A21-M2-B28	1A	3.19	418	
712	A22-M2-B28	1A	3.14	434	
713	A24-M2-B28	1A	3.61	432	20
714	A25-M2-B28	1A	3.82	446	
715	A26-M2-B28	1A	3.44	440	
716	A35-M2-B28	1A	3.46	432	
717	A33-M2-B28	1A	3.04	384	
718	A5-M2-B28	1A	3.18	438	
719	A28-M2-B28	1A	3.245	422	
720	A1-M2-B28	1A	3.09	404	
721	A8-M2-B28	1A	3.25	422	
722	A30-M2-B28	1A	3.51	436	
723	A17-M2-B29	1A	2.18	437	
724	A3-M2-B29	1A	1.76	371	
725	A19-M2-B29	1A	2.59	435	30
726	A32-M2-B29	1A	1.675	408	
727	A11-M2-B29	1A	2.09	451	
728	A26-M2-B29	1A	2.4	443	
729	A28-M2-B29	1A	2.21	425	
730	A8-M2-B29	1A	2.205	425	
731	A17-M2-B8	1A	2.95	420	
732	A31-M2-B8	1A	2.815	433	
733	A3-M2-B8	1A	2.52	354	
734	A19-M2-B8	1A	3.33	418	
735	A20-M2-B8	1A	2.88	408	
736	A32-M2-B8	1A	2.37	391	
737	A11-M2-B8	1A	2.86	434	
738	A21-M2-B8	1A	2.95	404	
739	A22-M2-B8	1A	2.91	420	
740	A4-M2-B8	1A	2.86	370	
741	A24-M2-B8	1A	3.4	418	
742	A25-M2-B8	1A	3.63	432	
743	A26-M2-B8	1A	3.22	426	
744	A35-M2-B8	1A	3.24	418	
745	A36-M2-B8	1A	2.98	438	
746	A33-M2-B8	1A	2.78	370	
747	A5-M2-B8	1A	2.94	424	
748	A27-M2-B8	1A	2.58	356	
749	A28-M2-B8	1A	3.01	408	
750	A1-M2-B8	1A	2.85	390	50
751	A8-M2-B8	1A	3.02	408	
752	A30-M2-B8	1A	3.295	422	
753	A17-M2-B10	1A	2.895	408	
754	A31-M2-B10	1A	2.74	421	
755	A18-M2-B10	1A	3.27	412	
756	A19-M2-B10	1A	3.3	406	
757	A20-M2-B10	1A	2.82	396	
758	A32-M2-B10	1A	2.28	379	
759	A11-M2-B10	1A	2.8	422	
760	A24-M2-B10	1A	3.37	406	
761	A26-M2-B10	1A	3.17	414	
762	A35-M2-B10	1A	3.2	406	
763	A33-M2-B10	1A	2.72	358	
764	A5-M2-B10	1A	2.88	412	
765	A28-M2-B10	1A	2.95	396	
766	A8-M2-B10	1A	2.96	396	
767	A30-M2-B10	1A	3.26	410	
768	A17-M2-B17	1A	3.1	422	
769	A31-M2-B17	1A	2.99	435	65
770	A18-M2-B17	1A	3.455	426	

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
771	A3-M2-B17	1A	2.71	356	
772	A32-M2-B17	1A	2.55	393	
773	A11-M2-B17	1A	3.03	436	
774	A21-M2-B17	1A	3.12	406	
775	A22-M2-B17	1A	3.07	422	
776	A4-M2-B17	1A	3.055	372	
777	A6-M2-B17	1A	3.195	422	5
778	A24-M2-B17	1A	3.54	420	
779	A26-M2-B17	1A	3.37	428	
780	A35-M2-B17	1A	3.38	420	
781	A36-M2-B17	1A	3.13	440	
782	A5-M2-B17	1A	3.1	426	
783	A27-M2-B17	1A	2.76	358	
784	A28-M2-B17	1A	3.17	410	10
785	A8-M2-B17	1A	3.18	410	
786	A30-M2-B17	1A	3.45	424	
787	A17-M2-B30	1A	2.79	406	
788	A31-M2-B30	1A	2.61	419	
789	A18-M2-B30	1A	3.16	410	
790	A19-M2-B30	1A	3.2	404	15
791	A32-M2-B30	1A	2.15	377	
792	A11-M2-B30	1A	2.67	420	
793	A4-M2-B30	1A	2.67	356	
794	A6-M2-B30	1A	2.86	406	
795	A24-M2-B30	1A	3.27	404	
796	A25-M2-B30	1A	3.53	418	20
797	A26-M2-B30	1A	3.05	412	
798	A35-M2-B30	1A	3.09	404	
799	A33-M2-B30	1A	2.58	356	
800	A27-M2-B30	1A	2.37	342	
801	A28-M2-B30	1A	2.84	394	
802	A30-M2-B30	1A	3.135	408	25
803	A17-M2-B3	1A	2.12	449	
804	A31-M2-B3	1A	1.99	462	
805	A18-M2-B3	1A	2.42	453	
806	A3-M2-B3	1A	1.69	383	
807	A37-M2-B3	1A	2.24	462	
808	A19-M2-B3	1A	2.52	447	30
809	A32-M2-B3	1A	1.61	420	
810	A11-M2-B3	1A	2.03	463	
811	A21-M2-B3	1A	2.075	433	
812	A24-M2-B3	1A	2.61	447	
813	A25-M2-B3	1A	2.87	461	
814	A26-M2-B3	1A	2.315	455	
815	A33-M2-B3	1A	1.92	399	35
816	A5-M2-B3	1A	2.05	453	
817	A34-M2-B3	1A	1.59	371	
818	A27-M2-B3	1A	1.715	385	
819	A28-M2-B3	1A	2.13	437	
820	A29-M2-B3	1A	1.47	357	
821	A1-M2-B3	1A	2.01	419	40
822	A8-M2-B3	1A	2.125	437	
823	A17-M2-B7	1A	2.715	436	
824	A31-M2-B7	1A	2.54	449	
825	A18-M2-B7	1A	3.08	440	
826	A19-M2-B7	1A	3.125	434	
827	A11-M2-B7	1A	2.61	450	45
828	A21-M2-B7	1A	2.7	420	
829	A24-M2-B7	1A	3.21	434	
830	A25-M2-B7	1A	3.46	448	
831	A26-M2-B7	1A	2.99	442	
832	A35-M2-B7	1A	3.02	434	
833	A36-M2-B7	1A	2.74	454	50
834	A33-M2-B7	1A	2.51	386	
835	A5-M2-B7	1A	2.67	440	
836	A34-M2-B7	1A	2.13	358	
837	A27-M2-B7	1A	2.31	372	
838	A28-M2-B7	1A	2.77	424	
839	A29-M2-B7	1A	1.97	344	
840	A8-M2-B7	1A	2.78	424	55
841	A30-M2-B7	1A	3.09	438	
842	A17-M2-B31	1A	2.32	477	
843	A31-M2-B31	1A	2.19	490	
844	A18-M2-B31	1A	2.59	481	
845	A3-M2-B31	1A	1.89	411	
846	A19-M2-B31	1A	2.67	475	60
847	A20-M2-B31	1A	2.21	465	

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
848	A32-M2-B31	1A	1.815	448	
849	A11-M2-B31	1A	2.22	491	
850	A4-M2-B31	1A	2.17	427	
851	A6-M2-B31	1A	2.385	477	
852	A23-M2-B31	1A	1.75	415	
853	A24-M2-B31	1A	2.77	475	
854	A26-M2-B31	1A	2.53	483	5
855	A5-M2-B31	1A	2.24	481	
856	A34-M2-B31	1A	1.795	399	
857	A28-M2-B31	1A	2.335	465	
858	A8-M2-B31	1A	2.34	465	
859	A17-M2-B32	1A	2.18	477	
860	A31-M2-B32	1A	2.05	490	
861	A18-M2-B32	1A	2.49	481	
862	A3-M2-B32	1A	1.76	411	
863	A37-M2-B32	1A	2.27	490	
864	A19-M2-B32	1A	2.575	475	
865	A32-M2-B32	1A	1.685	448	
866	A11-M2-B32	1A	2.08	491	15
867	A21-M2-B32	1A	2.16	461	
868	A4-M2-B32	1A	2.04	427	
869	A6-M2-B32	1A	2.27	477	
870	A23-M2-B32	1A	1.63	415	
871	A24-M2-B32	1A	2.64	475	
872	A25-M2-B32	1A	2.905	489	
873	A26-M2-B32	1A	2.39	483	25
874	A35-M2-B32	1A	2.44	475	
875	A36-M2-B32	1A	2.21	495	
876	A5-M2-B32	1A	2.13	481	
877	A28-M2-B32	1A	2.19	465	
878	A1-M2-B32	1A	2.06	447	
879	A8-M2-B32	1A	2.2	465	30
880	A17-M2-B33	1A	2.705	424	
881	A31-M2-B33	1A	2.54	437	
882	A3-M2-B33	1A	2.24	358	
883	A19-M2-B33	1A	3.13	422	
884	A20-M2-B33	1A	2.62	412	
885	A32-M2-B33	1A	2.085	395	
886	A11-M2-B33	1A	2.61	438	35
887	A21-M2-B33	1A	2.705	408	
888	A22-M2-B33	1A	2.66	424	
889	A4-M2-B33	1A	2.59	374	
890	A6-M2-B33	1A	2.795	424	
891	A24-M2-B33	1A	3.215	422	
892	A25-M2-B33	1A	3.47	436	
893	A26-M2-B33	1A	2.99	430	
894	A35-M2-B33	1A	3.03	422	
895	A36-M2-B33	1A	2.73	442	
896	A33-M2-B33	1A	2.51	374	
897	A5-M2-B33	1A	2.67	428	
898	A27-M2-B33	1A	2.3	360	45
899	A1-M2-B33	1A	2.59	394	
900	A8-M2-B33	1A	2.78	412	
901	A30-M2-B33	1A	3.085	426	
902	A17-M2-B34	1A	2.25	517	
903	A31-M2-B34	1A	2.11	530	
904	A18-M2-B34	1A	2.535	521	
905	A3-M2-B34	1A	1.83	451	
906	A19-M2-B34	1A	2.63	515	
907	A20-M2-B34	1A	2.15	505	
908	A32-M2-B34	1A	1.745	488	
909	A11-M2-B34	1A	2.13	531	
910	A21-M2-B34	1A	2.195	501	
911	A22-M2-B34	1A	2.2	517	
912	A4-M2-B34	1A	2.085	467	
913	A6-M2-B34	1A	2.33	517	
914	A24-M2-B34	1A	2.685	515	
915	A26-M2-B34	1A	2.43	523	
916	A35-M2-B34	1A	2.5	515	
917	A36-M2-B34	1A	2.255	535	
918	A33-M2-B34	1A	2.055	467	
919	A27-M2-B34	1A	1.855	453	
920	A28-M2-B34	1A	2.255	505	
921	A1-M2-B34	1A	2.115	487	
922	A8-M2-B34	1A	2.265	505	
923	A30-M2-B34	1A	2.555	519	60
924	A17-M2-B35	1A	2.36	512	

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
925	A31-M2-B35	1A	2.25	525	5
926	A18-M2-B35	1A	2.68	516	
927	A3-M2-B35	1A	1.95	446	
928	A37-M2-B35	1A	2.44	525	
929	A19-M2-B35	1A	2.73	510	
930	A20-M2-B35	1A	2.27	500	10
931	A32-M2-B35	1A	1.875	483	
932	A11-M2-B35	1A	2.27	526	
933	A4-M2-B35	1A	2.235	462	
934	A6-M2-B35	1A	2.435	512	
935	A24-M2-B35	1A	2.81	510	
936	A26-M2-B35	1A	2.57	518	
937	A35-M2-B35	1A	2.63	510	
938	A36-M2-B35	1A	2.395	530	
939	A28-M2-B35	1A	2.39	500	
940	A1-M2-B35	1A	2.265	482	15
941	A8-M2-B35	1A	2.39	500	
942	A30-M2-B35	1A	2.69	514	
943	A17-M2-B36	1A	2.83	406	
944	A31-M2-B36	1A	2.67	419	
945	A18-M2-B36	1A	3.205	410	
946	A27-M2-B43	1A	1.87	399	
947	A19-M2-B36	1A	3.245	404	
948	A20-M2-B36	1A	2.755	394	
949	A32-M2-B36	1A	2.215	377	
950	A22-M2-B36	1A	2.8	406	
951	A4-M2-B36	1A	2.74	356	
952	A6-M2-B36	1A	2.925	406	
953	A28-M2-B43	1A	2.27	451	
954	A24-M2-B36	1A	3.33	404	
955	A25-M2-B36	1A	3.565	418	
956	A26-M2-B36	1A	3.115	412	25
957	A35-M2-B36	1A	3.14	404	
958	A33-M2-B36	1A	2.63	356	
959	A5-M2-B36	1A	2.82	410	
960	A27-M2-B36	1A	2.44	342	
961	A28-M2-B36	1A	2.89	394	
962	A29-M2-B36	1A	2.07	314	
963	A1-M2-B36	1A	2.73	376	
964	A8-M2-B36	1A	2.895	394	
965	A30-M2-B36	1A	3.2	408	
966	A17-M2-B37	1A	2.15	463	30
967	A31-M2-B37	1A	476	1044	
968	A18-M2-B37	1A	2.445	467	
969	A19-M2-B37	1A	2.545	461	
970	A20-M2-B37	1A	2.03	451	
971	A32-M2-B37	1A	1.62	434	
972	A11-M2-B37	1A	477	1049	
973	A21-M2-B37	1A	2.095	447	
974	A4-M2-B37	1A	1.965	413	
975	A6-M2-B37	1A	2.225	463	
976	A24-M2-B37	1A	2.605	461	35
977	A25-M2-B37	1A	2.89	475	
978	A26-M2-B37	1A	2.335	469	
979	A35-M2-B37	1A	2.42	461	
980	A36-M2-B37	1A	2.15	481	
981	A33-M2-B37	1A	1.93	413	
982	A5-M2-B37	1A	2.08	467	
983	A27-M2-B37	1A	1.735	399	
984	A28-M2-B37	1A	2.13	451	
985	A29-M2-B37	1A	1.485	371	
986	A1-M2-B37	1A	2.01	433	40
987	A8-M2-B37	1A	2.135	451	
988	A17-M2-B38	1A	3.02	452	
989	A31-M2-B38	1A	2.88	465	
990	A18-M2-B38	1A	3.37	456	
991	A32-M2-B38	1A	2.44	423	
992	A11-M2-B38	1A	2.94	466	
993	A21-M2-B38	1A	3.035	436	
994	A22-M2-B38	1A	2.98	452	
995	A4-M2-B38	1A	2.94	402	
996	A26-M2-B38	1A	3.29	458	45
997	A35-M2-B38	1A	3.31	450	
998	A36-M2-B38	1A	3.06	470	
999	A5-M2-B38	1A	3.02	456	
1000	A34-M2-B38	1A	2.48	374	
1001	A27-M2-B38	1A	2.66	388	

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺
1002	A28-M2-B38	1A	3.08	440
1003	A8-M2-B38	1A	3.09	440
1004	A30-M2-B38	1A	3.37	454
1005	A17-M2-B39	1A	3.14	422
1006	A31-M2-B39	1A	3.02	435
1007	A18-M2-B39	1A	3.49	426
1008	A3-M2-B39	1A	2.76	356
1009	A19-M2-B39	1A	3.52	420
1010	A20-M2-B39	1A	3.09	410
1011	A32-M2-B39	1A	2.585	393
1012	A11-M2-B39	1A	3.055	436
1013	A22-M2-B39	1A	3.115	422
1014	A4-M2-B39	1A	3.1	372
1015	A6-M2-B39	1A	3.24	422
1016	A23-M2-B39	1A	2.53	360
1017	A24-M2-B39	1A	3.6	420
1018	A25-M2-B39	1A	3.81	434
1019	A26-M2-B39	1A	3.41	428
1020	A35-M2-B39	1A	3.44	420
1021	A36-M2-B39	1A	3.18	440
1022	A33-M2-B39	1A	3	372
1023	A5-M2-B39	1A	3.14	426
1024	A27-M2-B39	1A	2.82	358
1025	A28-M2-B39	1A	3.22	410
1026	A1-M2-B39	1A	3.07	392
1027	A8-M2-B39	1A	3.22	410
1028	A30-M2-B39	1A	3.48	424
1029	A19-M2-B40	1A	2.59	475
1030	A20-M2-B40	1A	2.08	465
1031	A32-M2-B40	1A	1.66	448
1032	A11-M2-B40	1A	2.07	491
1033	A21-M2-B40	1A	2.12	461
1034	A4-M2-B40	1A	2.005	427
1035	A24-M2-B40	1A	2.64	475
1036	A25-M2-B40	1A	2.89	489
1037	A26-M2-B40	1A	2.355	483
1038	A35-M2-B40	1A	2.43	475
1039	A36-M2-B40	1A	2.18	495
1040	A5-M2-B40	1A	2.11	481
1041	A27-M2-B40	1A	1.8	413
1042	A28-M2-B40	1A	2.165	465
1043	A1-M2-B40	1A	2.06	447
1044	A8-M2-B40	1A	2.175	465
1045	A30-M2-B40	1A	2.49	479
1046	A17-M2-B41	1A	2.98	420
1047	A18-M2-B41	1A	3.34	424
1048	A19-M2-B41	1A	3.38	418
1049	A32-M2-B41	1A	2.4	391
1050	A11-M2-B41	1A	2.895	434
1051	A21-M2-B41	1A	2.995	404
1052	A24-M2-B41	1A	3.445	418
1053	A25-M2-B41	1A	3.67	432
1054	A33-M2-B41	1A	2.81	370
1055	A5-M2-B41	1A	2.99	424
1056	A28-M2-B41	1A	3.055	408
1057	A1-M2-B41	1A	2.89	390
1058	A17-M2-B42	1A	3.18	434
1059	A31-M2-B42	1A	3.065	447
1060	A37-M2-B42	1A	3.24	447
1061	A19-M2-B42	1A	3.54	432
1062	A20-M2-B42	1A	3.13	422
1063	A32-M2-B42	1A	2.63	405
1064	A11-M2-B42	1A	3.095	448
1065	A21-M2-B42	1A	3.19	418
1066	A4-M2-B42	1A	3.13	384
1067	A6-M2-B42	1A	3.27	434
1068	A24-M2-B42	1A	3.6	432
1069	A26-M2-B42	1A	3.44	440
1070	A34-M2-B42	1A	2.68	356
1071	A28-M2-B42	1A	3.24	422
1072	A1-M2-B42	1A	3.09	404
1073	A8-M2-B42	1A	3.25	422
1074	A1-M2-B43	1A	2.125	433
1075	A17-M2-B46	1A	2.75	394
1076	A3-M2-B6	1A	2.27	328
1077	A19-M2-B6	1A	3.17	392
1078	A20-M2-B6	1A	2.67	382

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
1079	A32-M2-B6	1A	2.11	365	5
1080	A11-M2-B6	1A	2.63	408	
1081	A22-M2-B6	1A	2.7	394	
1082	A4-M2-B6	1A	2.63	344	
1083	A6-M2-B6	1A	2.83	394	
1084	A24-M2-B6	1A	3.25	392	10
1085	A26-M2-B6	1A	3.02	400	
1086	A33-M2-B6	1A	2.54	344	
1087	A5-M2-B6	1A	2.72	398	
1088	A28-M2-B6	1A	2.8	382	
1089	A8-M2-B43	1A	2.255	451	
1090	A17-M2-B43	1A	2.235	463	
1091	A31-M2-B43	1A	2.115	476	
1092	A18-M2-B43	1A	2.58	467	
1093	A3-M2-B43	1A	1.81	397	
1094	A19-M2-B43	1A	2.625	461	15
1095	A20-M2-B43	1A	2.145	451	
1096	A32-M2-B43	1A	1.725	434	
1097	A11-M2-B43	1A	2.14	477	
1098	A6-M2-B43	1A	2.34	463	
1099	A24-M2-B43	1A	2.705	461	
1100	A38-M2-B41	3	5.02	458	
1101	A39-M2-B8	3	5.28	432	
1102	A39-M2-B34	3	4.71	529	
1103	A45-M2-B24	1A	1.51	407	
1104	A41-M2-B24	1A	1.94	469	20
1105	A42-M2-B24	1A	1.59	421	
1106	A43-M2-B24	1A	2.31	501	
1107	A45-M2-B26	1A	1.74	401	
1108	A42-M2-B26	1A	1.84	415	
1109	A44-M2-B26	1A	2.43	499	
1110	A45-M2-B27	1A	2.46	366	
1111	A42-M2-B27	1A	2.56	380	
1112	A43-M2-B27	1A	3.33	460	
1113	A44-M2-B27	1A	3.16	464	
1114	A41-M2-B28	1A	3.07	440	25
1115	A43-M2-B28	1A	3.43	472	
1116	A44-M2-B28	1A	3.27	476	
1117	A45-M2-B29	1A	1.535	381	
1118	A42-M2-B29	1A	1.64	395	
1119	A44-M2-B29	1A	2.17	479	
1120	A45-M2-B8	1A	2.32	364	
1121	A41-M2-B8	1A	2.805	426	
1122	A42-M2-B8	1A	2.42	378	
1123	A43-M2-B8	1A	3.18	458	30
1124	A44-M2-B8	1A	3.01	462	
1125	A45-M2-B10	1A	2.23	352	
1126	A42-M2-B10	1A	2.35	366	
1127	A43-M2-B10	1A	3.13	446	
1128	A44-M2-B10	1A	2.97	450	
1129	A45-M2-B17	1A	2.505	366	35
1130	A41-M2-B17	1A	2.98	428	
1131	A42-M2-B17	1A	2.62	380	
1132	A43-M2-B17	1A	3.35	460	
1133	A44-M2-B17	1A	3.195	464	
1134	A45-M2-B30	1A	2.08	350	40
1135	A45-M2-B3	1A	1.47	393	
1136	A41-M2-B3	1A	1.91	455	
1137	A42-M2-B3	1A	1.56	407	
1138	A45-M2-B7	1A	2.03	380	
1139	A42-M2-B7	1A	2.13	394	
1140	A43-M2-B7	1A	2.92	474	
1141	A44-M2-B7	1A	2.76	478	45
1142	A45-M2-B31	1A	1.69	421	
1143	A44-M2-B31	1A	2.29	519	
1144	A45-M2-B32	1A	1.56	421	
1145	A41-M2-B32	1A	1.98	483	
1146	A42-M2-B32	1A	1.64	435	
1147	A43-M2-B32	1A	2.325	515	
1148	A44-M2-B32	1A	2.16	519	50
1149	A45-M2-B33	1A	2.01	368	
1150	A41-M2-B33	1A	2.53	430	
1151	A42-M2-B33	1A	2.125	382	
1152	A44-M2-B33	1A	2.75	466	
1153	A41-M2-B34	1A	2.03	523	
1154	A42-M2-B34	1A	1.705	475	
1155	A44-M2-B34	1A	2.21	559	

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
5	1156	A45-M2-B35	1A	1.775	456
	1157	A41-M2-B35	1A	2.205	518
	1158	A42-M2-B35	1A	1.865	470
	1159	A43-M2-B35	1A	2.55	550
	1160	A44-M2-B35	1A	2.385	554
	1161	A45-M2-B36	1A	2.14	350
	1162	A41-M2-B36	1A	2.68	412
	1163	A43-M2-B36	1A	3.08	444
	1164	A44-M2-B36	1A	2.89	448
	1165	A45-M2-B37	1A	1.5	407
	1166	A41-M2-B37	1A	1.93	469
	1167	A42-M2-B37	1A	1.57	421
	1168	A43-M2-B37	1A	2.265	501
	1169	A44-M2-B37	1A	2.1	505
	1170	A45-M2-B38	1A	2.39	396
	1171	A41-M2-B38	1A	2.89	458
	1172	A42-M2-B38	1A	2.505	410
	1173	A43-M2-B38	1A	3.27	490
	1174	A44-M2-B38	1A	3.11	494
	1175	A41-M2-B39	1A	3.035	428
	1176	A42-M2-B39	1A	2.64	380
	1177	A43-M2-B39	1A	3.39	460
	1178	A44-M2-B39	1A	3.23	464
	1179	A45-M2-B40	1A	1.545	421
	1180	A41-M2-B40	1A	1.95	483
	1181	A42-M2-B40	1A	1.63	435
	1182	A43-M2-B40	1A	2.27	515
	1183	A44-M2-B40	1A	2.13	519
	1184	A45-M2-B41	1A	2.35	364
	1185	A41-M2-B41	1A	2.855	426
	1186	A45-M2-B42	1A	2.59	378
	1187	A42-M2-B42	1A	2.68	392
	1188	A44-M2-B42	1A	3.26	476
	1189	A44-M2-B6	1A	2.78	436
	1190	A40-M1-B11	2	5.73	488
	1191	A41-M1-B24	1A	1.83	455
	1192	A42-M1-B24	1A	1.51	407
	1193	A43-M1-B24	1A	2.165	487
	1194	A44-M1-B24	1A	1.98	491
	1195	A45-M1-B25	1A	1.51	387
	1196	A42-M1-B25	1A	1.605	401
	1197	A45-M1-B26	1A	1.63	387
	1198	A42-M1-B26	1A	1.73	401
	1199	A44-M1-B26	1A	2.3	485
	1200	A45-M1-B27	1A	2.33	352
	1201	A41-M1-B27	1A	2.87	414
	1202	A42-M1-B27	1A	2.46	366
	1203	A43-M1-B27	1A	3.24	446
	1204	A44-M1-B27	1A	3.05	450
	1205	A45-M1-B28	1A	2.47	364
	1206	A41-M1-B28	1A	2.985	426
	1207	A42-M1-B28	1A	2.6	378
	1208	A43-M1-B28	1A	3.34	458
	1209	A44-M1-B28	1A	3.155	462
	1210	A42-M1-B29	1A	1.55	381
	1211	A44-M1-B29	1A	2.05	465
	1212	A45-M1-B8	1A	2.185	350
	1213	A41-M1-B8	1A	2.71	412
	1214	A42-M1-B8	1A	2.32	364
	1215	A43-M1-B8	1A	3.09	444
	1216	A44-M1-B8	1A	2.9	448
	1217	A45-M1-B10	1A	2.1	338
	1218	A41-M1-B10	1A	2.66	400
	1219	A42-M1-B10	1A	2.225	352
	1220	A43-M1-B10	1A	3.045	432
	1221	A44-M1-B10	1A	2.85	436
	1222	A45-M1-B17	1A	2.395	352
	1223	A41-M1-B17	1A	2.9	414
	1224	A42-M1-B17	1A	2.515	366
	1225	A43-M1-B17	1A	3.275	446
	1226	A44-M1-B17	1A	3.1	450
	1227	A45-M1-B30	1A	1.955	336
	1228	A42-M1-B30	1A	2.09	350
	1229	A43-M1-B30	1A	2.9	430
	1230	A44-M1-B30	1A	2.7	434
	1231	A41-M1-B3	1A	1.8	441
	1232	A42-M1-B3	1A	1.465	393

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
1233	A43-M1-B3	1A	2.135	473	5
1234	A44-M1-B3	1A	1.94	477	
1235	A45-M1-B7	1A	1.91	366	
1236	A41-M1-B7	1A	2.45	428	
1237	A42-M1-B7	1A	2.03	380	
1238	A43-M1-B7	1A	2.835	460	10
1239	A44-M1-B7	1A	2.63	464	
1240	A44-M1-B31	1A	2.18	505	
1241	A45-M1-B32	1A	1.485	407	
1242	A41-M1-B32	1A	1.89	469	
1243	A42-M1-B32	1A	1.56	421	
1244	A43-M1-B32	1A	2.21	501	
1245	A44-M1-B32	1A	2.045	505	
1246	A41-M1-B33	1A	2.425	416	
1247	A42-M1-B33	1A	2.02	368	
1248	A43-M1-B33	1A	2.82	448	15
1249	A44-M1-B33	1A	2.62	452	
1250	A41-M1-B34	1A	1.96	509	
1251	A43-M1-B34	1A	2.29	541	
1252	A44-M1-B34	1A	2.11	545	
1253	A45-M1-B35	1A	1.7	442	
1254	A41-M1-B35	1A	2.12	504	
1255	A42-M1-B35	1A	1.785	456	
1256	A43-M1-B35	1A	2.46	536	
1257	A44-M1-B35	1A	2.28	540	
1258	A45-M1-B36	1A	2.01	336	20
1259	A41-M1-B36	1A	2.595	398	
1260	A42-M1-B36	1A	2.15	350	
1261	A43-M1-B36	1A	2.98	430	
1262	A44-M1-B36	1A	2.77	434	
1263	A41-M1-B37	1A	1.82	455	
1264	A42-M1-B37	1A	1.5	407	
1265	A43-M1-B37	1A	2.18	487	
1266	A44-M1-B37	1A	1.965	491	
1267	A45-M1-B38	1A	2.29	382	
1268	A41-M1-B38	1A	2.83	444	25
1269	A42-M1-B38	1A	2.41	396	
1270	A43-M1-B38	1A	3.2	476	
1271	A44-M1-B38	1A	3.01	480	
1272	A45-M1-B39	1A	2.42	352	
1273	A41-M1-B39	1A	2.95	414	
1274	A42-M1-B39	1A	2.56	366	
1275	A43-M1-B39	1A	3.315	446	
1276	A44-M1-B39	1A	3.13	450	
1277	A45-M1-B40	1A	1.47	407	30
1278	A41-M1-B40	1A	1.865	469	
1279	A42-M1-B40	1A	1.55	421	
1280	A43-M1-B40	1A	2.2	501	
1281	A44-M1-B40	1A	2.005	505	
1282	A45-M1-B41	1A	2.225	350	
1283	A41-M1-B41	1A	2.765	412	35
1284	A42-M1-B41	1A	2.355	364	
1285	A43-M1-B41	1A	3.135	444	
1286	A44-M1-B41	1A	2.955	448	
1287	A45-M1-B42	1A	2.49	364	
1288	A41-M1-B42	1A	3	426	40
1289	A42-M1-B42	1A	2.6	378	
1290	A44-M1-B42	1A	3.19	462	
1291	A41-M1-B43	1A	2.48	386	
1292	A42-M1-B43	1A	2.04	338	
1293	A43-M1-B43	1A	2.88	418	
1294	A44-M1-B43	1A	2.67	422	
1295	A42-M1-B43	1A	1.61	407	45
1296	A44-M1-B43	1A	2.09	491	
1297	A46-M1-B24	1A	2.085	434	
1298	A47-M1-B24	1A	2.27	464	
1299	A48-M1-B24	1A	2.365	448	
1300	A49-M1-B24	1A	2.165	466	
1301	A50-M1-B24	1A	1.715	442	
1302	A51-M1-B24	1A	1.985	414	50
1303	A52-M1-B24	1A	1.465	372	
1304	A53-M1-B24	1A	1.58	416	
1305	A54-M1-B25	1A	2.445	434	
1306	A48-M1-B25	1A	2.495	442	
1307	A49-M1-B25	1A	2.285	460	
1308	A50-M1-B25	1A	1.815	436	55
1309	A51-M1-B25	1A	2.12	408	

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺
1310	A52-M1-B25	1A	1.535	366
1311	A53-M1-B25	1A	1.66	410
1312	A54-M1-B26	1A	2.655	434
1313	A46-M1-B26	1A	2.4	428
1314	A47-M1-B26	1A	2.57	458
1315	A48-M1-B26	1A	2.7	442
1316	A49-M1-B26	1A	2.495	460
1317	A50-M1-B26	1A	1.96	436
1318	A51-M1-B26	1A	2.3	408
1319	A52-M1-B26	1A	1.66	366
1320	A53-M1-B26	1A	1.79	410
1321	A54-M1-B27	1A	3.43	399
1322	A46-M1-B27	1A	3.19	393
1323	A47-M1-B27	1A	3.295	423
1324	A48-M1-B27	1A	3.455	407
1325	A49-M1-B27	1A	3.295	425
1326	A50-M1-B27	1A	2.68	401
1327	A51-M1-B27	1A	3.125	373
1328	A52-M1-B27	1A	2.345	331
1329	A53-M1-B27	1A	2.485	375
1330	A54-M1-B28	1A	3.53	411
1331	A46-M1-B28	1A	3.3	405
1332	A47-M1-B28	1A	3.38	435
1333	A48-M1-B28	1A	3.55	419
1334	A49-M1-B28	1A	3.39	437
1335	A50-M1-B28	1A	2.805	413
1336	A51-M1-B28	1A	3.24	385
1337	A52-M1-B28	1A	2.475	343
1338	A53-M1-B28	1A	2.625	387
1339	A54-M1-B29	1A	2.39	414
1340	A47-M1-B29	1A	2.295	438
1341	A48-M1-B29	1A	2.415	422
1342	A49-M1-B29	1A	2.225	440
1343	A50-M1-B29	1A	1.76	416
1344	A51-M1-B29	1A	2.045	388
1345	A53-M1-B29	1A	1.62	390
1346	A54-M1-B8	1A	3.27	397
1347	A46-M1-B8	1A	3.05	391
1348	A48-M1-B8	1A	3.305	405
1349	A49-M1-B8	1A	3.125	423
1350	A50-M1-B8	1A	2.52	399
1351	A51-M1-B8	1A	2.95	371
1352	A52-M1-B8	1A	2.185	329
1353	A53-M1-B8	1A	2.33	373
1354	A46-M1-B10	1A	2.98	379
1355	A47-M1-B10	1A	3.15	409
1356	A48-M1-B10	1A	3.26	393
1357	A49-M1-B10	1A	3.1	411
1358	A50-M1-B10	1A	2.46	387
1359	A51-M1-B10	1A	2.905	359
1360	A52-M1-B10	1A	2.11	317
1361	A53-M1-B10	1A	2.265	361
1362	A54-M1-B17	1A	3.45	399
1363	A46-M1-B17	1A	3.23	393
1364	A47-M1-B17	1A	3.32	423
1365	A48-M1-B17	1A	3.475	407
1366	A49-M1-B17	1A	3.305	425
1367	A50-M1-B17	1A	2.72	401
1368	A51-M1-B17	1A	3.15	373
1369	A53-M1-B17	1A	2.53	375
1370	A47-M1-B30	1A	2.97	407
1371	A48-M1-B30	1A	3.135	391
1372	A49-M1-B30	1A	2.945	409
1373	A50-M1-B30	1A	2.315	385
1374	A51-M1-B30	1A	2.75	357
1375	A52-M1-B30	1A	1.97	315
1376	A53-M1-B30	1A	2.125	359
1377	A54-M1-B3	1A	2.29	426
1378	A46-M1-B3	1A	2.06	420
1379	A47-M1-B3	1A	2.205	450
1380	A48-M1-B3	1A	2.345	434
1381	A49-M1-B3	1A	2.13	452
1382	A50-M1-B3	1A	1.68	428
1383	A51-M1-B3	1A	1.95	400
1384	A52-M1-B3	1A	1.415	358
1385	A53-M1-B3	1A	1.54	402
1386	A54-M1-B7	1A	3.02	413

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
1387	A46-M1-B7	1A	2.79	407	
1388	A48-M1-B7	1A	3.065	421	
1389	A49-M1-B7	1A	2.87	439	
1390	A50-M1-B7	1A	2.25	415	
1391	A51-M1-B7	1A	2.67	387	
1392	A52-M1-B7	1A	1.92	345	
1393	A53-M1-B7	1A	2.07	389	10
1394	A54-M1-B31	1A	2.52	454	
1395	A46-M1-B31	1A	2.28	448	
1396	A47-M1-B31	1A	2.43	478	
1397	A48-M1-B31	1A	2.525	462	
1398	A49-M1-B31	1A	2.345	480	
1399	A50-M1-B31	1A	1.89	456	15
1400	A51-M1-B31	1A	2.2	428	
1401	A52-M1-B31	1A	1.63	386	
1402	A53-M1-B31	1A	1.74	430	
1403	A54-M1-B32	1A	2.38	454	
1404	A46-M1-B32	1A	2.14	448	
1405	A47-M1-B32	1A	2.31	478	20
1406	A48-M1-B32	1A	2.415	462	
1407	A52-M1-B32	1A	1.515	386	
1408	A53-M1-B32	1A	1.635	430	
1409	A54-M1-B33	1A	3.03	401	
1410	A47-M1-B33	1A	2.89	425	
1411	A48-M1-B33	1A	3.06	409	
1412	A49-M1-B33	1A	2.86	427	25
1413	A50-M1-B33	1A	2.24	403	
1414	A51-M1-B33	1A	2.67	375	
1415	A52-M1-B33	1A	1.91	333	
1416	A53-M1-B33	1A	2.06	377	
1417	A54-M1-B34	1A	2.405	494	
1418	A47-M1-B34	1A	2.34	518	30
1419	A48-M1-B34	1A	2.47	502	
1420	A49-M1-B34	1A	2.28	520	
1421	A50-M1-B34	1A	1.84	496	
1422	A51-M1-B34	1A	2.1	468	
1423	A52-M1-B34	1A	1.58	426	
1424	A53-M1-B34	1A	1.69	470	35
1425	A54-M1-B35	1A	2.61	489	
1426	A48-M1-B35	1A	2.625	497	
1427	A49-M1-B35	1A	2.46	515	
1428	A50-M1-B35	1A	1.97	491	
1429	A51-M1-B35	1A	2.285	463	
1430	A52-M1-B35	1A	1.705	421	40
1431	A53-M1-B35	1A	1.82	465	
1432	A47-M1-B36	1A	3.06	407	
1433	A48-M1-B36	1A	3.21	391	
1434	A49-M1-B36	1A	3.03	409	
1435	A50-M1-B36	1A	2.39	385	
1436	A51-M1-B36	1A	2.85	357	45
1437	A52-M1-B36	1A	2.03	315	
1438	A53-M1-B36	1A	2.18	359	
1439	A54-M1-B37	1A	2.305	440	
1440	A47-M1-B37	1A	2.26	464	
1441	A48-M1-B37	1A	2.35	448	
1442	A49-M1-B37	1A	2.17	466	
1443	A50-M1-B37	1A	1.705	442	50
1444	A51-M1-B37	1A	1.975	414	
1445	A52-M1-B37	1A	1.45	372	
1446	A53-M1-B37	1A	1.57	416	
1447	A54-M1-B38	1A	3.39	429	
1448	A46-M1-B38	1A	3.14	423	
1449	A48-M1-B38	1A	3.4	437	55
1450	A49-M1-B38	1A	3.24	455	
1451	A50-M1-B38	1A	2.615	431	
1452	A51-M1-B38	1A	3.065	403	
1453	A52-M1-B38	1A	2.29	361	
1454	A53-M1-B38	1A	2.425	405	
1455	A54-M1-B39	1A	3.51	399	60
1456	A46-M1-B39	1A	3.27	393	
1457	A47-M1-B39	1A	3.365	423	
1458	A48-M1-B39	1A	3.53	407	
1459	A49-M1-B39	1A	3.36	425	
1460	A50-M1-B39	1A	2.78	401	
1461	A51-M1-B39	1A	3.22	373	65
1462	A52-M1-B39	1A	2.43	331	
1463	A53-M1-B39	1A	2.57	375	

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
5	1464	A54-M1-B40	1A	2.34	454
	1465	A47-M1-B40	1A	2.27	478
	1466	A48-M1-B40	1A	2.41	462
	1467	A49-M1-B40	1A	2.185	480
	1468	A50-M1-B40	1A	1.74	456
	1469	A51-M1-B40	1A	2.015	428
	1470	A52-M1-B40	1A	1.495	386
	1471	A53-M1-B40	1A	1.605	430
	1472	A54-M1-B41	1A	3.335	397
	1473	A46-M1-B41	1A	3.095	391
	1474	A47-M1-B41	1A	3.195	421
	1475	A48-M1-B41	1A	3.36	405
	1476	A49-M1-B41	1A	3.19	423
	1477	A50-M1-B41	1A	2.575	399
	1478	A51-M1-B41	1A	3.025	371
	1479	A52-M1-B41	1A	2.23	329
	1480	A53-M1-B41	1A	2.38	373
	1481	A54-M1-B42	1A	3.53	411
	1482	A46-M1-B42	1A	3.32	405
	1483	A48-M1-B42	1A	3.56	419
	1484	A49-M1-B42	1A	3.39	437
	1485	A50-M1-B42	1A	2.8	413
	1486	A51-M1-B42	1A	3.25	385
	1487	A52-M1-B42	1A	2.485	343
	1488	A53-M1-B42	1A	2.62	387
	1489	A46-M1-B6	1A	2.81	365
	1490	A47-M1-B6	1A	2.94	395
	1491	A48-M1-B6	1A	3.1	379
	1492	A49-M1-B6	1A	2.91	397
	1493	A50-M1-B6	1A	2.29	373
	1494	A51-M1-B6	1A	2.72	345
	1495	A52-M1-B6	1A	1.93	303
	1496	A53-M1-B6	1A	2.08	347
	1497	A54-M1-B43	1A	2.415	440
	1498	A48-M1-B43	1A	2.475	448
	1499	A49-M1-B43	1A	2.275	466
	1500	A51-M1-B43	1A	2.095	414
	1501	A53-M1-B43	1A	1.665	416
	1502	A54-M2-B24	1A	2.405	454
	1503	A46-M2-B24	1A	2.21	448
	1504	A47-M2-B24	1A	2.36	478
	1505	A48-M2-B24	1A	2.48	462
	1506	A49-M2-B24	1A	2.265	480
	1507	A50-M2-B24	1A	1.81	456
	1508	A51-M2-B24	1A	2.095	428
	1509	A52-M2-B24	1A	1.54	386
	1510	A53-M2-B24	1A	1.66	430
	1511	A54-M2-B25	1A	2.545	448
	1512	A48-M2-B25	1A	2.61	456
	1513	A49-M2-B25	1A	2.4	474
	1514	A51-M2-B25	1A	2.23	422
	1515	A52-M2-B25	1A	1.62	380
	1516	A54-M2-B26	1A	2.825	448
	1517	A46-M2-B26	1A	2.56	442
	1518	A47-M2-B26	1A	2.68	472
	1519	A48-M2-B26	1A	2.85	456
	1520	A49-M2-B26	1A	2.65	474
	1521	A50-M2-B26	1A	2.07	450
	1522	A51-M2-B26	1A	2.46	422
	1523	A52-M2-B26	1A	1.76	380
	1524	A54-M2-B27	1A	3.6	413
	1525	A46-M2-B27	1A	3.34	407
	1526	A47-M2-B27	1A	3.42	437
	1527	A48-M2-B27	1A	3.59	421
	1528	A49-M2-B27	1A	3.44	439
	1529	A50-M2-B27	1A	2.82	415
	1530	A51-M2-B27	1A	3.31	387
	1531	A52-M2-B27	1A	2.49	345
	1532	A53-M2-B27	1A	2.625	389
	1533	A54-M2-B28	1A	3.71	425
	1534	A46-M2-B28	1A	3.44	419
	1535	A47-M2-B28	1A	3.51	449
	1536	A48-M2-B28	1A	3.69	433
	1537	A49-M2-B28	1A	3.54	451
	1538	A50-M2-B28	1A	2.94	427
	1539	A51-M2-B28	1A	3.42	399
	1540	A52-M2-B28	1A	2.63	357

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
1541	A54-M2-B29	1A	2.45	428	
1542	A46-M2-B29	1A	2.25	422	
1543	A47-M2-B29	1A	2.4	452	
1544	A48-M2-B29	1A	2.53	436	
1545	A50-M2-B29	1A	1.86	430	
1546	A51-M2-B29	1A	2.145	402	
1547	A53-M2-B29	1A	1.71	404	5
1548	A54-M2-B8	1A	3.43	411	10
1549	A46-M2-B8	1A	3.185	405	
1550	A47-M2-B8	1A	3.26	435	
1551	A48-M2-B8	1A	3.425	419	
1552	A49-M2-B8	1A	3.25	437	
1553	A50-M2-B8	1A	2.645	413	15
1554	A51-M2-B8	1A	3.11	385	
1555	A52-M2-B8	1A	2.33	343	
1556	A53-M2-B8	1A	2.47	387	
1557	A54-M2-B10	1A	3.4	399	
1558	A46-M2-B10	1A	3.13	393	
1559	A47-M2-B10	1A	3.22	423	20
1560	A48-M2-B10	1A	3.41	407	
1561	A49-M2-B10	1A	3.225	425	
1562	A50-M2-B10	1A	2.6	401	
1563	A51-M2-B10	1A	3.08	373	
1564	A52-M2-B10	1A	2.25	331	
1565	A53-M2-B10	1A	2.4	375	
1566	A54-M2-B17	1A	3.61	413	25
1567	A46-M2-B17	1A	3.355	407	
1568	A47-M2-B17	1A	3.415	437	
1569	A48-M2-B17	1A	3.605	421	
1570	A49-M2-B17	1A	3.435	439	
1571	A50-M2-B17	1A	2.83	415	
1572	A51-M2-B17	1A	3.32	387	30
1573	A52-M2-B17	1A	2.52	345	
1574	A53-M2-B17	1A	2.65	389	
1575	A46-M2-B30	1A	3	391	
1576	A47-M2-B30	1A	3.08	421	
1577	A48-M2-B30	1A	3.27	405	
1578	A49-M2-B30	1A	3.08	423	35
1579	A50-M2-B30	1A	2.445	399	
1580	A51-M2-B30	1A	2.92	371	
1581	A46-M2-B3	1A	2.14	434	
1582	A48-M2-B3	1A	2.46	448	
1583	A49-M2-B3	1A	2.22	466	
1584	A50-M2-B3	1A	1.77	442	40
1585	A51-M2-B3	1A	2.07	414	
1586	A52-M2-B3	1A	1.495	372	
1587	A53-M2-B3	1A	1.62	416	
1588	A54-M2-B7	1A	3.16	427	
1589	A46-M2-B7	1A	2.9	421	
1590	A47-M2-B7	1A	3	451	
1591	A48-M2-B7	1A	3.19	435	45
1592	A49-M2-B7	1A	2.985	453	
1593	A50-M2-B7	1A	2.36	429	
1594	A51-M2-B7	1A	2.83	401	
1595	A53-M2-B7	1A	2.18	403	
1596	A47-M2-B31	1A	2.49	492	
1597	A49-M2-B31	1A	2.445	494	50
1598	A50-M2-B31	1A	1.97	470	
1599	A51-M2-B31	1A	2.28	442	
1600	A52-M2-B31	1A	1.7	400	
1601	A53-M2-B31	1A	1.83	444	
1602	A54-M2-B32	1A	2.48	468	
1603	A51-M2-B32	1A	2.16	442	55
1604	A54-M2-B33	1A	3.16	415	
1605	A46-M2-B33	1A	2.9	409	
1606	A47-M2-B33	1A	3	439	
1607	A48-M2-B33	1A	3.19	423	
1608	A49-M2-B33	1A	3	441	
1609	A50-M2-B33	1A	2.37	417	60
1610	A51-M2-B33	1A	2.82	389	
1611	A52-M2-B33	1A	2.025	347	
1612	A53-M2-B33	1A	2.17	391	
1613	A54-M2-B34	1A	2.495	508	
1614	A46-M2-B34	1A	2.29	502	
1615	A47-M2-B34	1A	2.42	532	65
1616	A48-M2-B34	1A	2.57	516	
1617	A49-M2-B34	1A	2.355	534	

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺	
1618	A50-M2-B34	1A	1.9	510	
1619	A51-M2-B34	1A	2.2	482	
1620	A52-M2-B34	1A	1.645	440	
1621	A53-M2-B34	1A	1.755	484	
1622	A54-M2-B35	1A	2.73	503	
1623	A46-M2-B35	1A	2.49	497	
1624	A47-M2-B35	1A	2.61	527	
1625	A48-M2-B35	1A	2.765	511	
1626	A49-M2-B35	1A	2.58	529	
1627	A50-M2-B35	1A	2.07	505	
1628	A51-M2-B35	1A	2.415	477	
1629	A52-M2-B35	1A	1.8	435	
1630	A53-M2-B35	1A	1.91	479	
1631	A47-M2-B36	1A	3.155	421	
1632	A48-M2-B36	1A	3.35	405	
1633	A49-M2-B36	1A	3.15	423	
1634	A50-M2-B36	1A	2.515	399	
1635	A51-M2-B36	1A	3	371	
1636	A52-M2-B36	1A	2.17	329	
1637	A53-M2-B36	1A	2.315	373	
1638	A46-M2-B37	1A	2.17	448	
1639	A47-M2-B37	1A	2.33	478	
1640	A48-M2-B37	1A	2.445	462	
1641	A49-M2-B37	1A	2.27	480	
1642	A50-M2-B37	1A	1.785	456	
1643	A51-M2-B37	1A	2.07	428	
1644	A52-M2-B37	1A	1.525	386	
1645	A53-M2-B37	1A	1.64	430	
1646	A54-M2-B38	1A	3.54	443	
1647	A46-M2-B38	1A	3.27	437	
1648	A47-M2-B38	1A	3.35	467	
1649	A48-M2-B38	1A	3.53	451	
1650	A49-M2-B38	1A	3.36	469	
1651	A50-M2-B38	1A	2.73	445	
1652	A51-M2-B38	1A	3.23	417	
1653	A52-M2-B38	1A	2.42	375	
1654	A53-M2-B38	1A	2.56	419	
1655	A54-M2-B39	1A	3.66	413	
1656	A46-M2-B39	1A	3.41	407	
1657	A47-M2-B39	1A	3.47	437	
1658	A48-M2-B39	1A	3.66	421	
1659	A49-M2-B39	1A	3.5	439	
1660	A50-M2-B39	1A	2.895	415	
1661	A51-M2-B39	1A	3.38	387	
1662	A52-M2-B39	1A	2.57	345	
1663	A53-M2-B39	1A	2.71	389	
1664	A54-M2-B40	1A	2.45	468	
1665	A46-M2-B40	1A	2.21	462	
1666	A47-M2-B40	1A	2.35	492	
1667	A48-M2-B40	1A	2.51	476	
1668	A49-M2-B40	1A	2.32	494	
1669	A50-M2-B40	1A	1.83	470	
1670	A51-M2-B40	1A	2.13	442	
1671	A52-M2-B40	1A	1.57	400	
1672	A53-M2-B40	1A	1.685	444	
1673	A54-M2-B41	1A	3.5	411	
1674	A46-M2-B41	1A	3.245	405	
1675	A47-M2-B41	1A	3.31	435	
1676	A49-M2-B41	1A	3.325	437	
1677	A50-M2-B41	1A	2.7	413	
1678	A51-M2-B41	1A	3.19	385	
1679	A52-M2-B41	1A	2.375	343	
1680	A53-M2-B41	1A	2.51	387	
1681	A54-M2-B42	1A	3.68	425	
1682	A46-M2-B42	1A	3.43	419	
1683	A47-M2-B42	1A	3.49	449	
1684	A48-M2-B42	1A	3.67	433	
1685	A49-M2-B42	1A	3.5	451	
1686	A50-M2-B42	1A	2.905	427	
1687	A52-M2-B42	1A	2.605	357	
1688	A53-M2-B42	1A	2.73	401	
1689	A54-M2-B46	1A	3.22	385	
1690	A47-M2-B46	1A	3.06	409	
1691	A48-M2-B43	1A	2.56	462	
1692	A48-M2-B6	1A	3.25	393	
1693	A49-M2-B6	1A	3.045	411	
1694	A49-M2-B43	1A	2.37	480	

TABLE III-continued

Entry	Compound	HPLC method	HPLC RT min	[M + H] ⁺
1695	A51-M2-B6	1A	2.88	359
1696	A52-M2-B43	1A	1.63	386
1697	A53-M2-B6	1A	2.21	361
1698	A47-M2-B43	1A	2.44	478

Example 10

Preparation of the 2,4-dimethyl-N-[1-methyl-8-(pyrrolidin-1-ylcarbonyl)-4,5-dihydro-1H-pyrazolo[4,3-g]indolizin-3-yl]benzamide (I)

After dissolving the compound 2,4-dimethyl-N-[8-(pyrrolidin-1-ylcarbonyl)-4,5-dihydro-1H-pyrazolo[4,3-g]indolizin-3-yl]benzamide (A35-M1-B8, Entry 200, Table III), obtained as described in the example 9, in dichloromethane 2 equivalent of methyl iodide were added. After four hours of stirring at room temperature, water was added and the phases were separated. The organic layer was Dried over Na₂SO₄ and the crude was purified through preparative HPLC. LCMS m/z 418 [M+H]⁺@ Rt 2.87 min.

1H NMR (DMSO-d6, 401 MHz): δ ppm=1.76-1.96 (m, 4 H), 2.32 (s, 3 H), 2.39 (s, 3 H), 2.86 (t, J=6.6 Hz, 2 H), 3.40-3.72 (m, 4 H), 4.09 (t, J=6.4 Hz, 2 H), 4.19 (s, 3H), 6.65 (br. s., 1 H), 7.04-7.14 (m, 2 H), 7.39 (br. s., 1 H), 7.40 (br. s., 1 H), 10.54 (br. s., 1 H).

The two possible tautomers were not isolated.

The invention claimed is:

1. A compound of formula (I):

2. A compound of formula (I) according to claim 1, wherein:

R1 is a group —CONHR^a wherein R^a is hydrogen or a group optionally substituted selected from straight or branched C₁-C₆ alkyl, straight or branched C₂-C₆ alkenyl, aryl and aryl C₁-C₆ alkyl.

3. A compound of formula (I) according to claim 1, wherein:

R1 is a group —COR^a wherein R^a is hydrogen or a group optionally substituted selected from straight or branched C₁-C₆ alkyl, straight or branched C₂-C₆ alkenyl, aryl and aryl C₁-C₆ alkyl.

4. A compound of formula (I) according to claim 1, wherein:

R1 is a group —SO₂R^a wherein R^a is hydrogen or a group optionally substituted selected from straight or branched C₁-C₆ alkyl, straight or branched C₂-C₆ alkenyl, aryl and aryl C₁-C₆ alkyl.

5. A compound of formula (I) according to any one of claims 1 to 4 wherein:

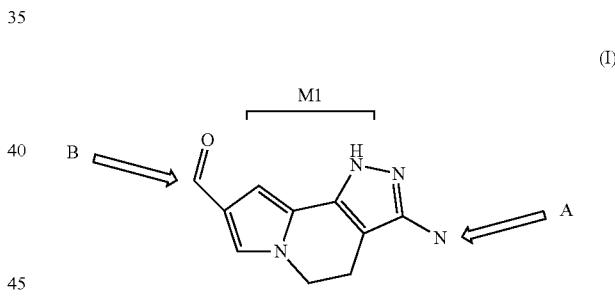
R2 is hydrogen.

6. A compound of formula (I) according to claim 1, wherein:

R3 is a group —NR^aR^b wherein both of R^a and R^b are hydrogen or one of them is a hydrogen and the remaining one of R^a or R^b is a group optionally substituted selected from straight or branched C₁-C₆ alkyl, straight or branched C₂-C₆ alkenyl, aryl and aryl C₁-C₆ alkyl.

7. A compound of formula (I) according to claim 1, wherein: R4 is hydrogen.

8. A compound of formula (I) according to claim 1, wherein R1 and R2, each independently one from the other, are a substituent denoted by any of codes A1-A54 and R3 is a substituent denoted by any of codes B1-B43 listed below, wherein the compounds have the formula:



wherein substituents A and B are:

FRAGMENT	CODE
M1	A1
	A2
	A3

wherein

n is 0;

R1, R2 and R4, each independently one from the other, are selected from the group consisting of —R^a, —COR^a, —CONHR^a, —SO₂R^a and —COOR^a;

R3 is a group —NR^aR^b or —OR^a;

wherein R^a and R^b, the same or different, are each independently hydrogen or a group optionally substituted, selected from straight or branched C₁-C₆ alkyl, straight or branched C₂-C₆ alkenyl, straight or branched C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, cycloalkyl C₁-C₆ alkyl, heterocycl, heterocycl C₁-C₆ alkyl, aryl, aryl C₁-C₆ alkyl, heteroaryl and heteroaryl C₁-C₆ alkyl or, taken together with the nitrogen atom to which they are bonded, either R^a and R^b, may form an optionally substituted 3 to 8 membered heterocycle, optionally containing one additional heteroatom or heteroatomic group selected from S, O, N or NH, and pharmaceutically acceptable salts thereof.

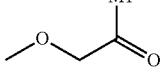
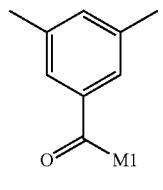
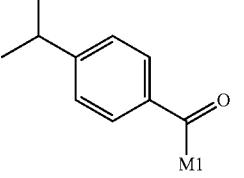
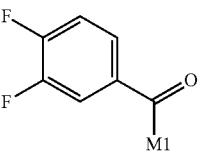
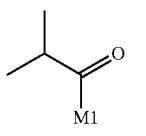
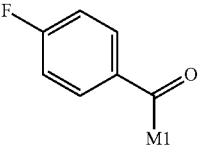
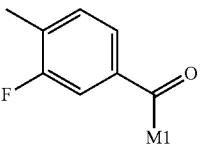
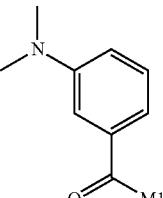
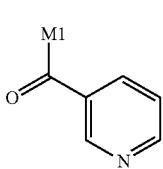
69
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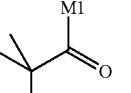
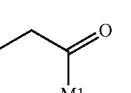
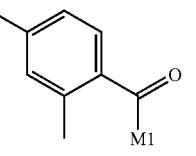
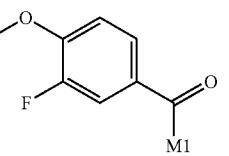
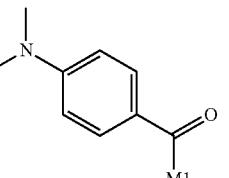
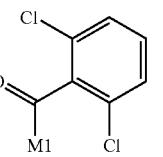
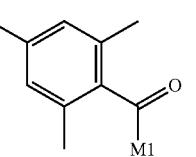
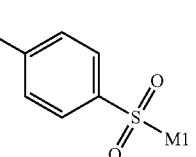
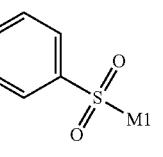
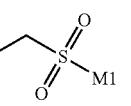
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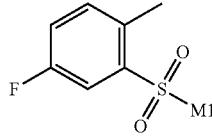
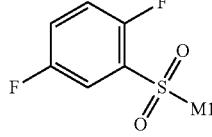
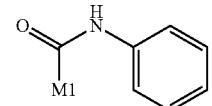
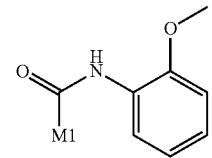
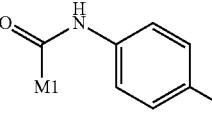
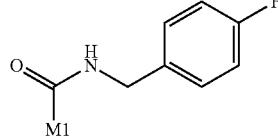
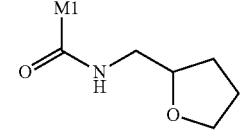
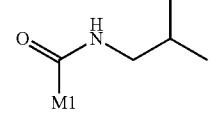
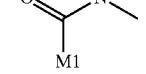
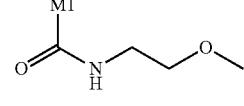
71
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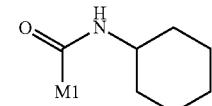
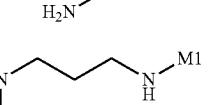
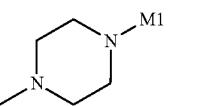
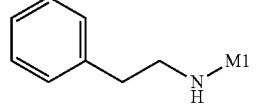
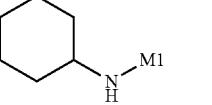
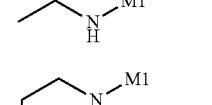
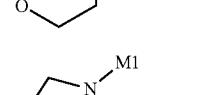
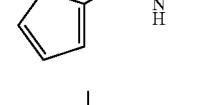
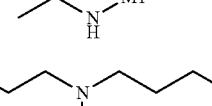
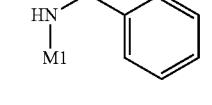
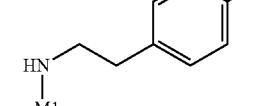
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FRAGMENT	CODE
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FRAGMENT	CODE
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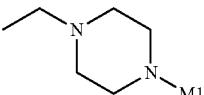
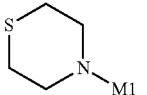
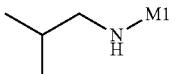
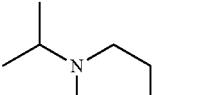
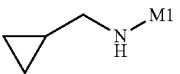
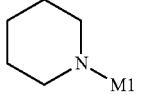
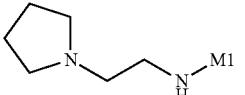
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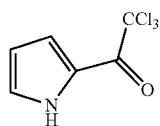
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FRAGMENT	CODE
	B37
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9. A process for preparing a compound of formula (I) as defined in claim 1, characterized in that the process comprises the following steps:

a) reaction of the compound of formula (II):



(II)
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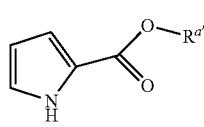
with an alcohol of formula (III):

R^{a'}-OH

(III)

wherein R^{a'} is straight or branched C₁-C₆ alkyl group;

b) acylation by Friedel-Craft reaction of the resultant compound of formula (IV):

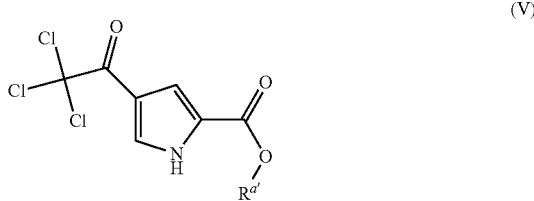


(IV) 60

wherein R^{a'} is as defined above;

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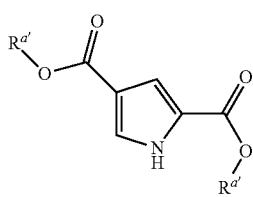
c) reaction of the resultant compound of formula (V):



(V)

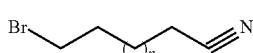
wherein R^{a'} is as defined above, with a suitable alcohol of formula (III) as defined above;

d) alkylation of the resultant compound of formula (VI):



(VI)

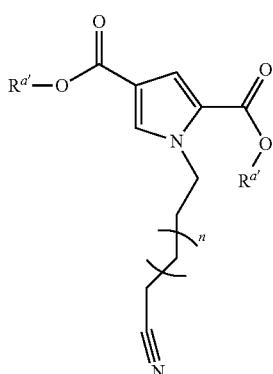
wherein both R^{a'}, each independently one from the other, are as defined above, with a suitable halo-cyanoalkane of formula (XXI):



(XXI)

wherein n is 0;

e) intramolecular condensation of the resultant compound of formula (VII):

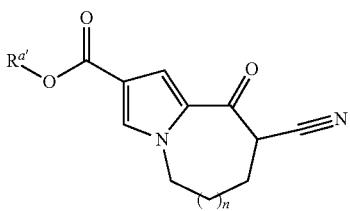


(VII)

wherein n is as defined above and both R^{a'}, each independently one from the other, are as defined above;

f) treatment with hydrazine or an hydrazine salt thereof, of the resultant compound of formula (VIII):

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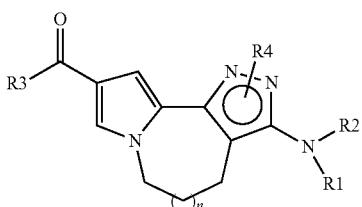


(VIII)

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wherein n and R^{a'} are as defined above, to give the compound of formula (I):



(I)

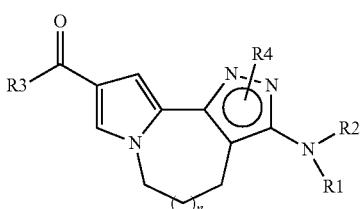
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wherein n is 0; R1, R2 and R4 are hydrogen and R3 is —OR^{a'}, wherein R^{a'} is a straight or branched C₁-C₆ alkyl group; optionally separating the resultant compound of formula (I) into the single isomers; and/or converting the resultant compound of formula (I) into a different compound of formula (I) by replacing the group —OR^{a'} with a different group which R3 represents, and/or by introducing the R4 group, and/or by derivatizing the amino moiety, and/or by removing the R4 group, and/or converting it into a pharmaceutically acceptable salt if desired.

10. A process according to claim 9, characterized in that the compound of formula (I)



(I)

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wherein n is 0; R1, R2 and R4 are hydrogen, and R3 is OR^{a'} wherein R^{a'} is straight or branched C₁-C₆ alkyl group, is optionally converted into a different compound of formula (I) according to one or more of the following reactions:

g) replacing the group —OR^{a'} with a different group which R3 represents, according to any one of the following reactions:

g.1) hydrolysis under basic condition to give the corresponding compound of formula (I) wherein R3 is OH, optionally followed by the coupling of the resultant compound with an amine of formula (IX):

RNR^{a' R^b}

(IX)

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wherein R^a and R^b, the same or different, are each independently hydrogen or a group optionally substituted,

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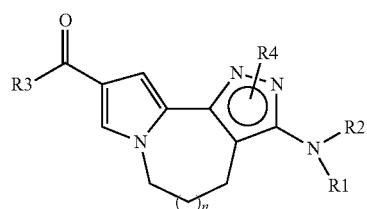
selected from straight or branched C₁-C₆ alkyl, straight or branched C₂-C₆ alkenyl, straight or branched C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, cycloalkyl C₁-C₆ alkyl, heterocycl, heterocycl C₁-C₆ alkyl, aryl, aryl C₁-C₆ alkyl, heteroaryl and heteroaryl C₁-C₆ alkyl or, taken together with the nitrogen atom to which they are bonded, either R^a and R^b, may form an optionally substituted 3 to 8 membered heterocycle, optionally containing one additional heteroatom or heteroatomic group selected from S, O, N or NH, to give the corresponding compound of formula (I) wherein R3 is —NR^{a' R^b, and R^a and R^b are as defined above, or g.2) transesterification by reactions with a compound of formula (III) as defined above, to give the corresponding compound of formula (I) wherein R3 is OR^{a'} and R^{a'} is a different C₁-C₆ alkyl, or g.3) coupling with an amine of formula (IX):}

HNR^{a' R^b}

(IX)

wherein R^a and R^b are as defined above, to give the corresponding compound of formula (I) wherein R3 is —NR^{a' R^b, and R^a and R^b are as defined above; or}

h) introducing the group R4 into the resultant compound of formula (I):



(I)

wherein n is defined above and R3 is a group —NR^{a' R^b or —OR^{a'}, and R1, R2 and R4 are hydrogen, according to any one of the following reactions:}

h.1) coupling with an equivalent of an halide of formula (X):

R^{a' Z}

(X)

wherein R^a is as defined above but not hydrogen and Z is a halogen, to give the corresponding compound of formula (I) wherein R4 is R^a, and R^a is as defined above but not hydrogen, or h.2) coupling with an equivalent of an acyl halide of formula (XI):

R^{a' COZ}

(XI)

wherein R^a and Z are as defined above, to give the corresponding compound of formula (I) wherein R4 is —COR^{a'} and R^a is as defined above, or

h.3) coupling with an equivalent of an alkoxy carbonyl halide of formula (XII):

R^{a' OCOZ}

(XII)

wherein R^a and Z are as defined above, to give the corresponding compound of formula (I) wherein R4 is —OCOR^{a'} and R^a is as defined above, or

h.4) coupling with an equivalent of a sulfonyl halide of formula (XIII):

R^{a' SO₂Z}

(XIII)

wherein R^a and Z are as defined above, to give the corresponding compound of formula (I) wherein R4 is

81

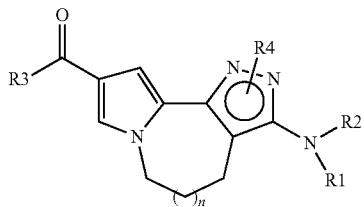
$\text{--SO}_2\text{R}^a$ and R^a is as defined above, or h.5) coupling with an equivalent of an isocyanate of formula (XIV):



(XIV)

wherein R^a is as defined above, to give the corresponding compound of formula (I) wherein $\text{R}4$ is --CONHR^a and R^a is as defined above; or

i) derivatizing the amino moiety of the resultant compound of formula (I):



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wherein n and $\text{R}3$ are as defined in formula (I), and $\text{R}1$, $\text{R}2$ and $\text{R}4$ are hydrogen, according to any one of the following reactions:

i.1) coupling with an equivalent of an acyl halide of formula (XI):



(XI)

wherein R^a is as defined above and Z is a halogen, to give the corresponding compound of formula (I) wherein one of $\text{R}1$ or $\text{R}2$ is hydrogen and the other one is --COR^a and R^a is as defined above, or

i.2) coupling with an equivalent of an alkoxy carbonyl halide of formula (XII):



(XII)

wherein R^a and Z are as defined above, to give the corresponding compound of formula (I) wherein one of $\text{R}1$ or $\text{R}2$ is hydrogen and the other one is --OCOR^a and R^a is as defined above, or

i.3) coupling with an equivalent of a sulfonyl halide of formula (XIII):



(XIII)

wherein R^a and Z are as defined above, to give the corresponding compound of formula (I) wherein one of $\text{R}1$ or $\text{R}2$ is hydrogen and the other one is $\text{--SO}_2\text{R}^a$ is as defined above, or

i.4) coupling with an equivalent of an isocyanate of formula (XIV):



(XIV)

wherein R^a is as defined above, to give the corresponding compound of formula (I) wherein one of $\text{R}1$ or $\text{R}2$ is hydrogen and the other one is --CONHR^a and R^a is as defined above, or

i.5) coupling with an equivalent of a carbonyl compound of formula (XV):

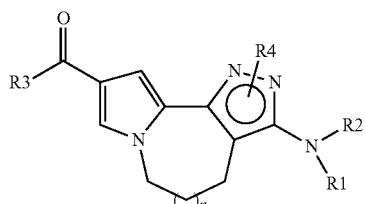


(XV)

wherein R^a and R^b are as defined above, to give the corresponding compound of formula (I) wherein one of $\text{R}1$ or $\text{R}2$ is hydrogen and the other one is --COR^a and R^a is as defined above; or

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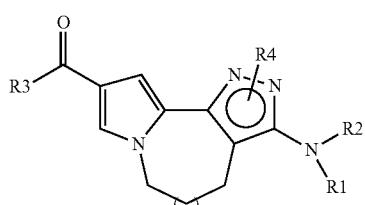
j) further derivatizing the amino moiety of the resultant compound of formula (I):



(I)

wherein n and $\text{R}3$ are as defined above; one of $\text{R}1$ and $\text{R}2$ is hydrogen and the other is selected from the group consisting of --R^a , --COR^a , --CONHR^a , $\text{--SO}_2\text{R}^a$ and --COOR^a , but not hydrogen, and $\text{R}4$ is selected from the group consisting of --R^a , --COR^a , --CONHR^a , $\text{--SO}_2\text{R}^a$ and --COOR^a , but not hydrogen, according to any one of the reactions described under steps 1.1) to i.5) above; or

k) removing the group $\text{R}4$ from the resultant compound of formula (I):



(I)

wherein n , $\text{R}1$, $\text{R}2$ and $\text{R}3$ are as defined above and $\text{R}4$ is as defined above but not hydrogen, by treatment with a basic solution, to obtain the corresponding compound wherein $\text{R}4$ is hydrogen;

optionally separating the resultant compound of formula (I) into the single isomers, and/or converting the resultant compound of formula (I) into a pharmaceutically acceptable salt.

11. A process for preparing a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, which process comprises the following steps:

i) acylation of the alkoxy carbonyl derivative of formula (I) wherein n is as defined in claim 1;

R1, $\text{R}2$ and $\text{R}4$ are hydrogen, and R^a is straight or branched $\text{C}_1\text{--C}_6$ alkyl group, with trifluoroacetic anhydride;

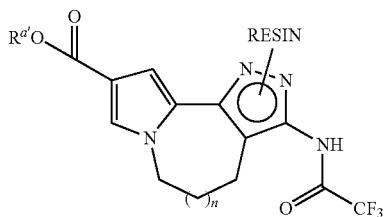
m) removal from the resultant compound of formula (I) of the trifluoroacetyl group in position 1 or 2 of the pyrrolidine ring;

n) loading of the resultant compound of formula (I) trifluoroacetylated in position 3 onto a resin as suitable solid support;

o) hydrolyzing under acid or basic conditions the resultant compound of formula (XVI)

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(XVI)



5

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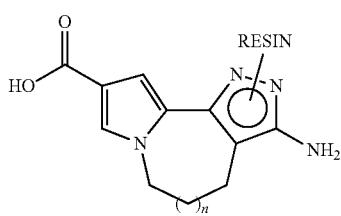
wherein n is as defined in claim 1, R^{a'} is as defined above and the resin is a polystyrenic resin selected from the group consisting of Br-Wang resin, Trityl resin, Cl-trityl resin, Merrifield resin, MAMP resin, isocyanate resin and derivatives thereof;

p) coupling the carboxyl group of the resultant compound of formula (XVII):

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(XVII)



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wherein n and the resin are as defined above, with an amine of formula (IX);

HNR^aR^b

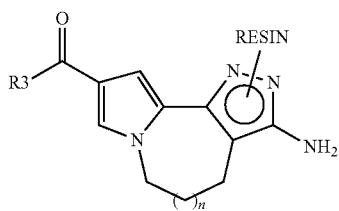
(IX)

35

q) derivatizing the amino moiety in position 3 of resultant compound of formula (XVIII):

40

(XVIII)



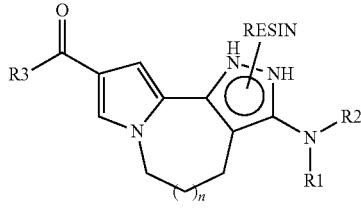
45

wherein n and the resin are as defined above, with an amine of formula (IX) as defined above;

r) cleaving the resin from the resultant compound of formula (XIX):

55

(XIX)



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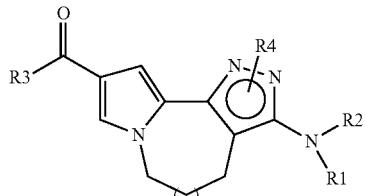
so as to obtain the desired compounds of formula I, optionally converting the resultant compound of formula (I)

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into a different compound of formula (I) and/or converting it into a pharmaceutically acceptable salt if desired.

12. Two or more compounds of formula (I):

(I)



wherein

n is 0;

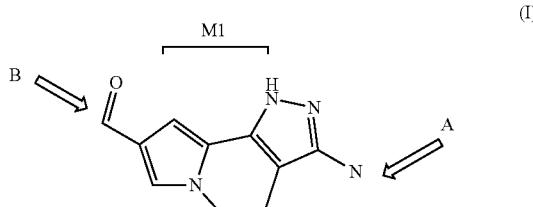
R1, R2 and R4, each independently one from the other, are selected from the group consisting of —R^a, —COR^a, —CONHR^a, —SO₂R^a and —COOR^a;

R3 is a group —NR^aR^b or —OR^a;

wherein R^a and R^b, the same or different, are each independently hydrogen or a group optionally substituted, selected from straight or branched C₁-C₆ alkyl, straight or branched C₂-C₆ alkenyl, straight or branched C₂-C₆ alkynyl, C₃-C₅ cycloalkyl, cycloalkyl C₁-C₆ alkyl, heterocyclyl, heterocyclyl C₁-C₆ alkyl, aryl, aryl C₁-C₆ alkyl, heteroaryl and heteroaryl C₁-C₆ alkyl or, taken together with the nitrogen atom to which they are bonded, either R^a and R^b, may form an optionally substituted 3 to 8 membered heterocycle, optionally containing one additional heteroatom or heteroatomic group selected from S, O, N or NH,

and pharmaceutically acceptable salts thereof.

13. Two or more compounds according to claim 12, wherein the compounds have the formula:



wherein substituents A and B are:

FRAGMENT	CODE
M1	A1
M1	A2

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-continued

FRAGMENT	CODE
	A3
	A4
	A5
	A6
	A7
	A8
	A9
	A10
	A11
	A12

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-continued

FRAGMENT	CODE
	A13
	A14
	A15
	A16
	A17
	A18
	A19
	A20
	A21

87
-continued

FRAGMENT	CODE
	A22
	A23
	A24
	A25
	A26
	A27
	A28
	A29
	A30
	A31

88
-continued

FRAGMENT	CODE
	A32
	A33
	A34
	A35
	A36
	A37
	A38
	A39
	A40
	A41

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-continued

FRAGMENT	CODE
	A42
	A43
	A44
	A45
	A46
	A47
	A48
	A49
	A50
	A51
	A52

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-continued

FRAGMENT	CODE
	A53
	A54
	B1
	B2
	B3
	B4
	B5
	B6
	B7
	B8
	B9
	B10
	B11
	B12

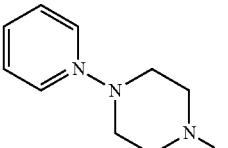
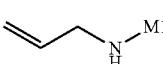
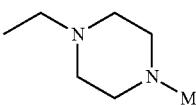
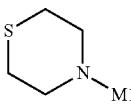
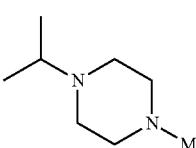
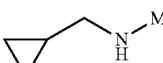
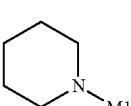
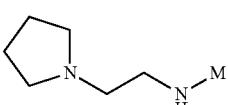
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-continued

FRAGMENT	CODE
	B13
	B14
	B15
	B16
	B17
	B18
	B19
	B20
	B21
	B22
	B23

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-continued

FRAGMENT	CODE
	B24
	B25
	B26
	B27
	B28
	B29
	B30
	B31
	B32
	B33
	B34

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-continued

FRAGMENT	CODE	
	B35	5
	B36	10
	B37	15
	B38	20
	B39	25
	B40	30
	B41	35
	B42	40
	B43,	45

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-continued

Entry	Compound
19	A14-M1-B12
20	A15-M1-B12
21	A12-M1-B12
22	A13-M1-B12
23	A14-M1-B13
24	A15-M1-B13
25	A8-M1-B13
26	A9-M1-B13
27	A15-M1-B11
28	A8-M1-B12
29	A9-M1-B12
30	A10-M1-B12
31	A11-M1-B12
32	A10-M1-B13
33	A11-M1-B13
34	A12-M1-B13
35	A13-M1-B13
36	A14-M1-B14
37	A15-M1-B14
38	A8-M1-B14
39	A9-M1-B14
40	A10-M1-B14
41	A11-M1-B14
42	A12-M1-B14
43	A13-M1-B14
44	A14-M1-B15
45	A15-M1-B15
46	A8-M1-B15
47	A9-M1-B15
48	A10-M1-B15
49	A11-M1-B15
50	A12-M1-B15
51	A13-M1-B15
52	A14-M1-B16
53	A15-M1-B16
54	A8-M1-B16
55	A13-M1-B16
56	A9-M1-B16
57	A10-M1-B16
58	A11-M1-B16
59	A12-M1-B16
60	A14-M1-B11
61	A16-M1-B10
62	A16-M1-B17
63	A16-M1-B18
64	A16-M1-B19
65	A1-M1-B20
66	A1-M1-B21
67	A1-M1-B22
68	A1-M1-B23
69	A17-M1-B24
70	A18-M1-B24
71	A3-M1-B24
72	A19-M1-B24
73	A20-M1-B24
74	A11-M1-B24
75	A21-M1-B24
76	A22-M1-B24
77	A4-M1-B24
78	A6-M1-B24
79	A23-M1-B24
80	A24-M1-B24
81	A25-M1-B24
82	A26-M1-B24
83	A27-M1-B24
84	A28-M1-B24
85	A29-M1-B24
86	A8-M1-B24
87	A30-M1-B24
88	A17-M1-B25
89	A31-M1-B25
90	A18-M1-B25
91	A3-M1-B25
92	A19-M1-B25
93	A20-M1-B25
94	A32-M1-B25
95	A11-M1-B25

and wherein the compounds are among those listed herein below:

Entry	Compound	
1	A1-M1-B1	50
2	A2-M1-B1	
3	A3-M1-B1	
4	A1-M1-B2	
5	A1-M1-B3	
6	A1-M1-B4	
7	A1-M1-B5	
8	A1-M1-B6	
9	A4-M1-B7	
10	A5-M1-B8	
11	A6-M1-B9	55
12	A7-M1-B10	
13	A8-M1-B11	
14	A9-M1-B11	
15	A10-M1-B11	
16	A11-M1-B11	
17	A12-M1-B11	60
18	A13-M1-B11	

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-continued

Entry	Compound
96	A21-M1-B25
97	A24-M1-B25
98	A26-M1-B25
99	A33-M1-B25
100	A5-M1-B25
101	A27-M1-B25
102	A28-M1-B25
103	A29-M1-B25
104	A1-M1-B25
105	A8-M1-B25
106	A17-M1-B26
107	A31-M1-B26
108	A18-M1-B26
109	A3-M1-B26
110	A19-M1-B26
111	A20-M1-B26
112	A32-M1-B26
113	A11-M1-B26
114	A21-M1-B26
115	A22-M1-B26
116	A6-M1-B26
117	A24-M1-B26
118	A26-M1-B26
119	A33-M1-B26
120	A5-M1-B26
121	A34-M1-B26
122	A27-M1-B26
123	A28-M1-B26
124	A1-M1-B26
125	A8-M1-B26
126	A17-M1-B27
127	A31-M1-B27
128	A18-M1-B27
129	A3-M1-B27
130	A19-M1-B27
131	A20-M1-B27
132	A32-M1-B27
133	A21-M1-B27
134	A6-M1-B27
135	A23-M1-B27
136	A24-M1-B27
137	A25-M1-B27
138	A26-M1-B27
139	A35-M1-B27
140	A33-M1-B27
141	A5-M1-B27
142	A28-M1-B27
143	A1-M1-B27
144	A8-M1-B27
145	A30-M1-B27
146	A17-M1-B28
147	A31-M1-B28
148	A18-M1-B28
149	A3-M1-B28
150	A19-M1-B28
151	A20-M1-B28
152	A32-M1-B28
153	A11-M1-B28
154	A21-M1-B28
155	A4-M1-B28
156	A6-M1-B28
157	A23-M1-B28
158	A24-M1-B28
159	A26-M1-B28
160	A35-M1-B28
161	A36-M1-B28
162	A33-M1-B28
163	A5-M1-B28
164	A28-M1-B28
165	A29-M1-B28
166	A1-M1-B28
167	A8-M1-B28
168	A30-M1-B28
169	A17-M1-B29
170	A18-M1-B29
171	A3-M1-B29
172	A20-M1-B29

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-continued

Entry	Compound
5	A32-M1-B29
10	A11-M1-B29
15	A21-M1-B29
20	A22-M1-B29
25	A4-M1-B29
30	A6-M1-B29
35	A24-M1-B29
40	A26-M1-B29
45	A33-M1-B29
50	A36-M1-B29
55	A32-M1-B29
60	A3-M1-B29
65	A11-M1-B29

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-continued

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-continued

Entry	Compound		Entry	Compound
250	A8-M1-B17		327	A4-M1-B31
251	A30-M1-B17	5	328	A24-M1-B31
252	A17-M1-B30		329	A26-M1-B31
253	A31-M1-B30		330	A33-M1-B31
254	A19-M1-B30		331	A5-M1-B31
255	A20-M1-B30		332	A27-M1-B31
256	A32-M1-B30		333	A28-M1-B31
257	A21-M1-B30	10	334	A29-M1-B31
258	A22-M1-B30		335	A1-M1-B31
259	A4-M1-B30		336	A8-M1-B31
260	A24-M1-B30		337	A17-M1-B32
261	A25-M1-B30		338	A31-M1-B32
262	A26-M1-B30		339	A18-M1-B32
263	A35-M1-B30	15	340	A37-M1-B32
264	A36-M1-B30		341	A19-M1-B32
265	A33-M1-B30		342	A20-M1-B32
266	A5-M1-B30		343	A32-M1-B32
267	A28-M1-B30		344	A11-M1-B32
268	A1-M1-B30		345	A21-M1-B32
269	A8-M1-B30	20	346	A4-M1-B32
270	A30-M1-B30		347	A6-M1-B32
271	A17-M1-B3		348	A24-M1-B32
272	A31-M1-B3		349	A25-M1-B32
273	A18-M1-B3		350	A26-M1-B32
274	A3-M1-B3		351	A35-M1-B32
275	A37-M1-B3	25	352	A36-M1-B32
276	A19-M1-B3		353	A33-M1-B32
277	A20-M1-B3		354	A5-M1-B32
278	A32-M1-B3		355	A27-M1-B32
279	A11-M1-B3		356	A28-M1-B32
280	A21-M1-B3		357	A1-M1-B32
281	A22-M1-B3		358	A8-M1-B32
282	A4-M1-B3	30	359	A30-M1-B32
283	A6-M1-B3		360	A17-M1-B33
284	A24-M1-B3		361	A31-M1-B33
285	A25-M1-B3		362	A3-M1-B33
286	A26-M1-B3		363	A19-M1-B33
287	A36-M1-B3		364	A20-M1-B33
288	A34-M1-B3	35	365	A32-M1-B33
289	A27-M1-B3		366	A11-M1-B33
290	A28-M1-B3		367	A21-M1-B33
291	A29-M1-B3		368	A22-M1-B33
292	A8-M1-B3		369	A4-M1-B33
293	A30-M1-B3		370	A24-M1-B33
294	A17-M1-B7	40	371	A25-M1-B33
295	A31-M1-B7		372	A26-M1-B33
296	A3-M1-B7		373	A35-M1-B33
297	A19-M1-B7		374	A36-M1-B33
298	A20-M1-B7		375	A33-M1-B33
299	A32-M1-B7		376	A5-M1-B33
300	A11-M1-B7	45	377	A27-M1-B33
301	A21-M1-B7		378	A28-M1-B33
302	A22-M1-B7		379	A1-M1-B33
303	A6-M1-B7		380	A8-M1-B33
304	A24-M1-B7		381	A30-M1-B33
305	A25-M1-B7		382	A17-M1-B34
306	A26-M1-B7		383	A31-M1-B34
307	A35-M1-B7	50	384	A18-M1-B34
308	A36-M1-B7		385	A3-M1-B34
309	A33-M1-B7		386	A19-M1-B34
310	A5-M1-B7		387	A20-M1-B34
311	A34-M1-B7		388	A32-M1-B34
312	A27-M1-B7		389	A11-M1-B34
313	A28-M1-B7	55	390	A21-M1-B34
314	A29-M1-B7		391	A22-M1-B34
315	A8-M1-B7		392	A4-M1-B34
316	A30-M1-B7		393	A6-M1-B34
317	A17-M1-B31		394	A24-M1-B34
318	A31-M1-B31		395	A25-M1-B34
319	A18-M1-B31	60	396	A26-M1-B34
320	A3-M1-B31		397	A35-M1-B34
321	A19-M1-B31		398	A36-M1-B34
322	A20-M1-B31		399	A33-M1-B34
323	A32-M1-B31		400	A5-M1-B34
324	A11-M1-B31		401	A27-M1-B34
325	A21-M1-B31	65	402	A28-M1-B34
326	A22-M1-B31		403	A29-M1-B34

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-continued

Entry	Compound	
404	A8-M1-B34	
405	A30-M1-B34	5
406	A17-M1-B35	
407	A31-M1-B35	
408	A18-M1-B35	
409	A37-M1-B35	
410	A19-M1-B35	
411	A32-M1-B35	10
412	A11-M1-B35	
413	A22-M1-B35	
414	A4-M1-B35	
415	A6-M1-B35	
416	A25-M1-B35	
417	A26-M1-B35	15
418	A35-M1-B35	
419	A36-M1-B35	
420	A5-M1-B35	
421	A27-M1-B35	
422	A28-M1-B35	
423	A29-M1-B35	20
424	A1-M1-B35	
425	A8-M1-B35	
426	A30-M1-B35	
427	A17-M1-B36	
428	A31-M1-B36	
429	A18-M1-B36	
430	A3-M1-B36	25
431	A19-M1-B36	
432	A32-M1-B36	
433	A11-M1-B36	
434	A21-M1-B36	
435	A22-M1-B36	
436	A6-M1-B36	30
437	A24-M1-B36	
438	A25-M1-B36	
439	A26-M1-B36	
440	A35-M1-B36	
441	A36-M1-B36	
442	A33-M1-B36	35
443	A5-M1-B36	
444	A34-M1-B36	
445	A27-M1-B36	
446	A28-M1-B36	
447	A1-M1-B36	
448	A8-M1-B36	40
449	A30-M1-B36	
450	A17-M1-B37	
451	A31-M1-B37	
452	A18-M1-B37	
453	A3-M1-B37	
454	A19-M1-B37	45
455	A20-M1-B37	
456	A32-M1-B37	
457	A11-M1-B37	
458	A21-M1-B37	
459	A22-M1-B37	
460	A4-M1-B37	
461	A6-M1-B37	50
462	A24-M1-B37	
463	A25-M1-B37	
464	A26-M1-B37	
465	A36-M1-B37	
466	A33-M1-B37	
467	A5-M1-B37	55
468	A27-M1-B37	
469	A28-M1-B37	
470	A29-M1-B37	
471	A8-M1-B37	
472	A30-M1-B37	
473	A17-M1-B38	60
474	A31-M1-B38	
475	A3-M1-B38	
476	A19-M1-B38	
477	A20-M1-B38	
478	A32-M1-B38	
479	A11-M1-B38	65
480	A21-M1-B38	

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Entry	Compound
481	A22-M1-B38
482	A4-M1-B38
483	A6-M1-B38
484	A24-M1-B38
485	A25-M1-B38
486	A26-M1-B38
487	A35-M1-B38
488	A36-M1-B38
489	A5-M1-B38
490	A27-M1-B38
491	A28-M1-B38
492	A1-M1-B38
493	A8-M1-B38
494	A30-M1-B38
495	A17-M1-B39
496	A31-M1-B39
497	A3-M1-B39
498	A19-M1-B39
499	A20-M1-B39
500	A32-M1-B39
501	A11-M1-B39
502	A21-M1-B39
503	A22-M1-B39
504	A4-M1-B39
505	A6-M1-B39
506	A24-M1-B39
507	A25-M1-B39
508	A26-M1-B39
509	A35-M1-B39
510	A36-M1-B39
511	A33-M1-B39
512	A5-M1-B39
513	A34-M1-B39
514	A27-M1-B39
515	A28-M1-B39
516	A1-M1-B39
517	A8-M1-B39
518	A30-M1-B39
519	A17-M1-B40
520	A31-M1-B40
521	A3-M1-B40
522	A19-M1-B40
523	A20-M1-B40
524	A32-M1-B40
525	A11-M1-B40
526	A21-M1-B40
527	A22-M1-B40
528	A4-M1-B40
529	A6-M1-B40
530	A24-M1-B40
531	A25-M1-B40
532	A26-M1-B40
533	A35-M1-B40
534	A36-M1-B40
535	A33-M1-B40
536	A5-M1-B40
537	A34-M1-B40
538	A27-M1-B40
539	A28-M1-B40
540	A29-M1-B40
541	A1-M1-B40
542	A8-M1-B40
543	A30-M1-B40
544	A17-M1-B41
545	A31-M1-B41
546	A18-M1-B41
547	A3-M1-B41
548	A19-M1-B41
549	A20-M1-B41
550	A32-M1-B41
551	A11-M1-B41
552	A21-M1-B41
553	A22-M1-B41
554	A4-M1-B41
555	A6-M1-B41
556	A24-M1-B41
557	A25-M1-B41

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Entry	Compound
558	A26-M1-B41
559	A35-M1-B41
560	A33-M1-B41
561	A5-M1-B41
562	A27-M1-B41
563	A28-M1-B41
564	A1-M1-B41
565	A30-M1-B41
566	A17-M1-B42
567	A18-M1-B42
568	A19-M1-B42
569	A32-M1-B42
570	A11-M1-B42
571	A22-M1-B42
572	A4-M1-B42
573	A24-M1-B42
574	A25-M1-B42
575	A26-M1-B42
576	A35-M1-B42
577	A36-M1-B42
578	A5-M1-B42
579	A34-M1-B42
580	A27-M1-B42
581	A28-M1-B42
582	A1-M1-B42
583	A8-M1-B42
584	A30-M1-B42
585	A17-M1-B6
586	A31-M1-B6
587	A18-M1-B6
588	A3-M1-B6
589	A19-M1-B6
590	A20-M1-B6
591	A32-M1-B6
592	A11-M1-B6
593	A6-M1-B6
594	A24-M1-B6
595	A25-M1-B6
596	A26-M1-B6
597	A35-M1-B6
598	A36-M1-B6
599	A33-M1-B6
600	A5-M1-B6
601	A28-M1-B6
602	A8-M1-B6
603	A30-M1-B6
604	A17-M1-B43
605	A18-M1-B43
606	A19-M1-B43
607	A32-M1-B43
608	A11-M1-B43
609	A21-M1-B43
610	A22-M1-B43
611	A6-M1-B43
612	A24-M1-B43
613	A26-M1-B43
614	A33-M1-B43
615	A5-M1-B43
616	A28-M1-B43
617	A1-M1-B43
618	A8-M1-B43
619	A38-M1-B41
620	A39-M1-B8
621	A39-M1-B34
1190	A40-M1-B11
1191	A41-M1-B24
1192	A42-M1-B24
1193	A43-M1-B24
1194	A44-M1-B24
1195	A45-M1-B25
1196	A42-M1-B25
1197	A45-M1-B26
1198	A42-M1-B26
1199	A44-M1-B26
1200	A45-M1-B27
1201	A41-M1-B27
1202	A42-M1-B27

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Entry	Compound
5	A43-M1-B27
1203	A44-M1-B27
1204	A45-M1-B28
1205	A41-M1-B28
1206	A42-M1-B28
1207	A43-M1-B28
1208	A44-M1-B28
1209	A44-M1-B28
10	A42-M1-B29
1210	A44-M1-B29
1211	A45-M1-B29
1212	A41-M1-B8
1213	A42-M1-B8
1214	A42-M1-B8
1215	A43-M1-B8
15	A44-M1-B8
1216	A45-M1-B10
1217	A41-M1-B10
1218	A42-M1-B10
1219	A43-M1-B10
1220	A43-M1-B10
1221	A44-M1-B10
20	A45-M1-B17
1222	A41-M1-B17
1223	A42-M1-B17
1224	A43-M1-B17
1225	A44-M1-B17
1226	A44-M1-B17
1227	A45-M1-B30
1228	A42-M1-B30
1229	A43-M1-B30
25	A44-M1-B30
1230	A44-M1-B30
1231	A41-M1-B3
1232	A42-M1-B3
1233	A43-M1-B3
1234	A44-M1-B3
30	A45-M1-B7
1235	A41-M1-B7
1236	A42-M1-B7
1237	A43-M1-B7
1238	A44-M1-B7
1239	A44-M1-B7
1240	A44-M1-B31
35	A45-M1-B32
1241	A41-M1-B32
1242	A42-M1-B32
1243	A43-M1-B32
1244	A44-M1-B32
1245	A44-M1-B32
1246	A41-M1-B33
40	A42-M1-B33
1247	A43-M1-B33
1248	A44-M1-B33
1249	A41-M1-B34
1250	A43-M1-B34
1251	A44-M1-B34
1252	A44-M1-B34
1253	A45-M1-B35
45	A41-M1-B35
1254	A42-M1-B35
1255	A43-M1-B35
1256	A44-M1-B35
1257	A44-M1-B35
1258	A45-M1-B36
1259	A41-M1-B36
50	A42-M1-B36
1260	A43-M1-B36
1261	A44-M1-B36
1262	A44-M1-B36
1263	A41-M1-B37
1264	A42-M1-B37
1265	A43-M1-B37
55	A44-M1-B37
1266	A45-M1-B38
1267	A41-M1-B38
1268	A42-M1-B38
1269	A43-M1-B38
1270	A44-M1-B38
1271	A44-M1-B38
60	A45-M1-B39
1272	A41-M1-B39
1273	A42-M1-B39
1274	A43-M1-B39
1275	A44-M1-B39
1276	A44-M1-B39
65	A45-M1-B40
1277	A41-M1-B40
1278	A42-M1-B40
1279	A42-M1-B40

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Entry	Compound	
1280	A43-M1-B40	
1281	A44-M1-B40	
1282	A45-M1-B41	
1283	A41-M1-B41	
1284	A42-M1-B41	
1285	A43-M1-B41	
1286	A44-M1-B41	
1287	A45-M1-B42	5
1288	A41-M1-B42	
1289	A42-M1-B42	
1290	A44-M1-B42	
1291	A41-M1-B6	
1292	A42-M1-B6	
1293	A43-M1-B6	10
1294	A44-M1-B6	
1295	A42-M1-B43	
1296	A44-M1-B43	
1297	A46-M1-B24	
1298	A47-M1-B24	
1299	A48-M1-B24	15
1300	A49-M1-B24	
1301	A50-M1-B24	
1302	A51-M1-B24	
1303	A52-M1-B24	
1304	A53-M1-B24	
1305	A54-M1-B25	
1306	A48-M1-B25	20
1307	A49-M1-B25	
1308	A50-M1-B25	
1309	A51-M1-B25	
1310	A52-M1-B25	
1311	A53-M1-B25	
1312	A54-M1-B26	25
1313	A46-M1-B26	
1314	A47-M1-B26	
1315	A48-M1-B26	
1316	A49-M1-B26	
1317	A50-M1-B26	
1318	A51-M1-B26	30
1319	A52-M1-B26	
1320	A53-M1-B26	
1321	A54-M1-B27	
1322	A46-M1-B27	
1323	A47-M1-B27	
1324	A48-M1-B27	35
1325	A49-M1-B27	
1326	A50-M1-B27	
1327	A51-M1-B27	
1328	A52-M1-B27	
1329	A53-M1-B27	
1330	A54-M1-B28	40
1331	A46-M1-B28	
1332	A47-M1-B28	
1333	A48-M1-B28	
1334	A49-M1-B28	
1335	A50-M1-B28	
1336	A51-M1-B28	
1337	A52-M1-B28	45
1338	A53-M1-B28	
1339	A54-M1-B29	
1340	A47-M1-B29	
1341	A48-M1-B29	
1342	A49-M1-B29	
1343	A50-M1-B29	50
1344	A51-M1-B29	
1345	A53-M1-B29	
1346	A54-M1-B8	
1347	A46-M1-B8	
1348	A48-M1-B8	
1349	A49-M1-B8	55
1350	A50-M1-B8	
1351	A51-M1-B8	
1352	A52-M1-B8	
1353	A53-M1-B8	
1354	A46-M1-B10	60
1355	A47-M1-B10	
1356	A48-M1-B10	

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-continued

Entry	Compound	
1357	A49-M1-B10	
1358	A50-M1-B10	
1359	A51-M1-B10	
1360	A52-M1-B10	
1361	A53-M1-B10	
1362	A54-M1-B17	
1363	A46-M1-B17	
1364	A47-M1-B17	5
1365	A48-M1-B17	
1366	A49-M1-B17	
1367	A50-M1-B17	
1368	A51-M1-B17	
1369	A53-M1-B17	
1370	A47-M1-B30	10
1371	A48-M1-B30	
1372	A49-M1-B30	
1373	A50-M1-B30	
1374	A51-M1-B30	
1375	A52-M1-B30	
1376	A53-M1-B30	
1377	A54-M1-B3	15
1378	A46-M1-B3	
1379	A47-M1-B3	
1380	A48-M1-B3	
1381	A49-M1-B3	
1382	A50-M1-B3	
1383	A51-M1-B3	
1384	A52-M1-B3	
1385	A53-M1-B3	
1386	A54-M1-B7	
1387	A46-M1-B7	
1388	A48-M1-B7	
1389	A49-M1-B7	20
1390	A50-M1-B7	
1391	A51-M1-B7	
1392	A52-M1-B7	
1393	A53-M1-B7	
1394	A54-M1-B31	
1395	A46-M1-B31	
1396	A47-M1-B31	25
1397	A48-M1-B31	
1398	A49-M1-B31	
1399	A50-M1-B31	
1400	A51-M1-B31	
1401	A52-M1-B31	
1402	A53-M1-B31	
1403	A54-M1-B32	
1404	A46-M1-B32	
1405	A47-M1-B32	30
1406	A48-M1-B32	
1407	A52-M1-B32	
1408	A53-M1-B32	
1409	A54-M1-B33	
1410	A47-M1-B33	
1411	A48-M1-B33	
1412	A49-M1-B33	
1413	A50-M1-B33	
1414	A51-M1-B33	35
1415	A52-M1-B33	
1416	A53-M1-B33	
1417	A54-M1-B34	
1418	A47-M1-B34	
1419	A48-M1-B34	
1420	A49-M1-B34	
1421	A50-M1-B34	40
1422	A51-M1-B34	
1423	A52-M1-B34	
1424	A53-M1-B34	
1425	A54-M1-B35	
1426	A48-M1-B35	
1427	A49-M1-B35	45
1428	A50-M1-B35	
1429	A51-M1-B35	
1430	A52-M1-B35	
1431	A53-M1-B35	
1432	A47-M1-B36	
1433	A48-M1-B36	50

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-continued

Entry	Compound
1434	A49-M1-B36
1435	A50-M1-B36
1436	A51-M1-B36
1437	A52-M1-B36
1438	A53-M1-B36
1439	A54-M1-B37
1440	A47-M1-B37
1441	A48-M1-B37
1442	A49-M1-B37
1443	A50-M1-B37
1444	A51-M1-B37
1445	A52-M1-B37
1446	A53-M1-B37
1447	A54-M1-B38
1448	A46-M1-B38
1449	A48-M1-B38
1450	A49-M1-B38
1451	A50-M1-B38
1452	A51-M1-B38
1453	A52-M1-B38
1454	A53-M1-B38
1455	A54-M1-B39
1456	A46-M1-B39
1457	A47-M1-B39
1458	A48-M1-B39
1459	A49-M1-B39
1460	A50-M1-B39
1461	A51-M1-B39
1462	A52-M1-B39
1463	A53-M1-B39
1464	A54-M1-B40
1465	A47-M1-B40
1466	A48-M1-B40
1467	A49-M1-B40
1468	A50-M1-B40
1469	A51-M1-B40
1470	A52-M1-B40
1471	A53-M1-B40
1472	A54-M1-B41
1473	A46-M1-B41
1474	A47-M1-B41

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Entry	Compound
5	A48-M1-B41
1475	A49-M1-B41
1476	A50-M1-B41
1477	A51-M1-B41
1478	A52-M1-B41
1479	A53-M1-B41
1480	A54-M1-B42
1481	A46-M1-B42
1482	A48-M1-B42
1483	A49-M1-B42
1484	A50-M1-B42
1485	A51-M1-B42
1486	A52-M1-B42
1487	A53-M1-B42
1488	A46-M1-B6
1489	A47-M1-B6
1490	A48-M1-B6
1491	A49-M1-B6
1492	A50-M1-B6
1493	A51-M1-B6
1494	A52-M1-B6
1495	A53-M1-B6
1496	A54-M1-B43
1497	A48-M1-B43
1498	A49-M1-B43
1499	A50-M1-B43
1500	A51-M1-B43
1501	A53-M1-B43.

14. A method for treating a disease caused by and/or associated with a dysregulated protein kinase activity, selected from the group consisting of breast carcinoma, ovarian carcinoma and fibrosarcoma, which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as defined in claim 1.

15. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) as defined in claim 1, and, at least, one pharmaceutically acceptable excipient, carrier and/or diluent.

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